Electrophilic fluorinatíon of ethers and deactivated benzene derivatives

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A Thesis Entitled

Electrophilic fluorination of ethers and deactivated benzene derivatives

Submitted by

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Memorandum

The work described within this thesis was carried out at the University of Durham between January 2002 and December 2004. This thesis is the work of the author, except where acknowledge by reference and has not been submitted for any other degree. The copyright of this thesis lies solely with the author and no quotation from it should be published without prior written consent and information derived from it should be acknowledged.

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1. Versatile electrophilic fluorination methodology. RSC Fluorine Chemistry group, postgraduate symposium, University of Durham, Durham, UK.

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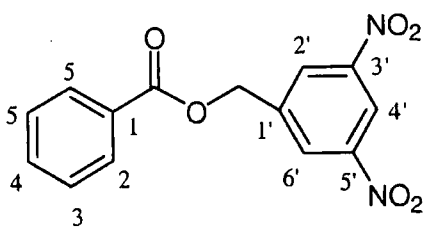
3. Versatile electrophilic flourination methodology. Poster session; 14th European symposium of fluorine chemistry, Poznan, Poland.

Abbreviations

The following abbreviations have been employed:

DCM	Dichloromethane
CFC	Chlorofluorocarbon
DAST	(diethylamino)sulfur trifluoride
GC-MS	Gas Chromatography-Mass Spectrometry
IR	Infrared
MR	Microreactor
NMR	Nuclear Magnetic Resonance
TLC	Thin Layer Chromatography
THF	Tetrahydrofuran
PTFCE	Polytrifluorochloroethylene
PTFE	Polytetrafluoroethylene
s	singlet in NMR spectrum
d	doublet in NMR spectrum
t	triplet in NMR spectrum
q	quartet in NMR spectrum
m	multiplet in NMR spectrum

Numbering of the system



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Abstract

Chapter 1 - Chapter 1 provides a literature review of the relevant topics for this thesis in organofluorine chemistry: effect of fluorine as a substituent on the molecule, synthesis of C-F bond from C-H bond using electrophilic reagents with discussions of mechanisms.

Chapter 2 - Direct fluorination of electron-rich systems such as alkyl and cyclic saturated ethers using elemental fluorine results in the formation of unexpected products: fluorinated aldal acetals. Selectfluor™ was also used to prepare these products in good yield, but also to gain information about mechanism.

Chapter 3 - Same methodology for fluorination of deactivated benzene derivatives using elemental fluorine was applied and resulted in a selective substitution of hydrogen by fluorine and allowed the synthesis of a diverse collection of polyfunctional monofluorinated aromatic products.

Chapter 4 - Fluorination of 1,3- and 1,4-disubstituted benzaldehyde derivatives was studied in the reactions with elemental fluorine and resulted usually in mixtures of two products. It is concluded that the distribution of the two competing products is dependent on the total electric effect of the substituent (σ-value) attached to the aromatic ring.

Chapter 5 - Our research group has developed a microreactor for the purpose of selective fluorination of a wide range of compounds such as benzaldehydes and nitrobenzenes. Low inventories of fluorine gas, in contact with reagents, provide increased safety. Optimization was obtained by varying substrate flow rate, and often resulted in a good conversion and superior yields.

Chapter 6-9- Experimental details of the work discussed in Chapters 2-5.

Content

Chapter 1 Introduction

1.1 Aim

This thesis is concerned with the synthesis of fluorinated organic compounds using electrophilic fluorinating agents: elemental fluorine and Selectfluor™. The introduction provides a literature review of the key concepts from organofluorine chemistry for this work. In particular, it introduces various fluorinating agents that have been developed so far for the synthesis of C-F bond.

1.2 Historical preview

The name "Fluorine" is derived from the Latin word *fleure* meaning flow, alluding to the flux power of the mineral fluorite (CaF_2), the most abundant compound of this element.

The first time elemental fluorine was identified by Karl W. Sheele in 1771 when preparing hydrofluoric acid. Although Frèmy in 1856 succeeded to liberate fluorine gas by electrolysis of molten salts, such as calcium fluoride and potassium fluoride, corrosion of the electrode did not allow the process to occur for any length of time, therefore Henry Moisson is often considered as the first person to isolate fluorine. In 1886, he developed a method (Figure 1.1) capable of producing an appreciable amount of gas. He used a diluted solution of potassium fluoride in anhydrous hydrofluoric acid and platinum or platinum-iridium alloy electrodes.[1]

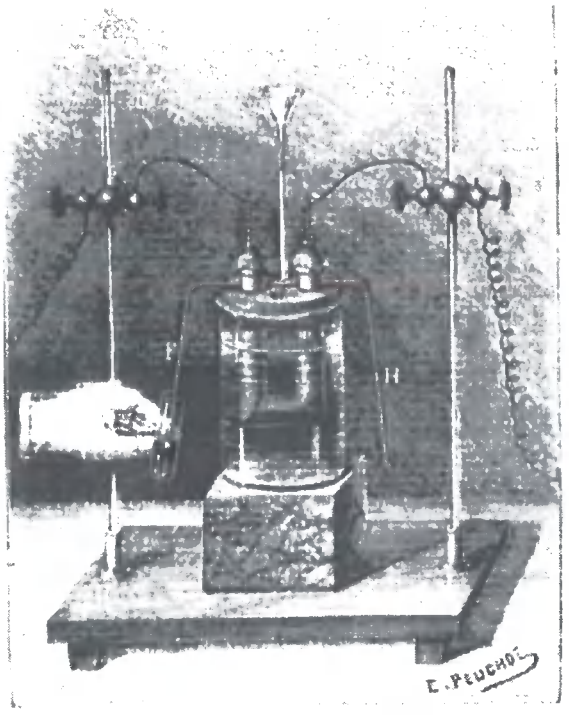


Figure 1.1 First apparatus for isolation of elemental fluorine[2]

The first organofluorine compounds were prepared by the Belgian chemist Swarts around 1890 by exchange reaction of activated carbon-chlorine compounds.

Forty years later, industrial scale preparation of fluorinated organic compounds began, with the production of chlorofluorocarbons as suitable replacement of methylchloride and ammonia for household refrigeration. An important point in the production of organofluorine compounds was during the Second World War with the Manhattan project, when a range of stable, highly resistant lubricants and coolants for handling highly corrosive uranium hexafluoride (UF_6) were developed. Later, production of these materials evolved into the fluorochemical and fluoropolymer material industry, with mainly civilian applications.

1.3 Abundance of fluorine in nature

Fluorine is the first element of the halogen family and in nature occurs as a pure mono-isotope ^{19}F. Furthermore, fluorine is the most abundant halogen element, about 0.07% of the earth crust is comprised of fluorine, mostly in the minerals cryolith (Na_3AlF_6) and

fluorospar (CaF_2). Despite this fact, organofluorine compounds are very rarely found in the biosphere. Speculated reasons for this phenomenon could be the very poor solubility of CaF_2, but also the very high hydration enthalpy of the small fluoride anion. This can decrease significantly the nucleophilicity of the fluorine anion in aqueous media and demands energy for the dehydration step.[2]

The first identified naturally occurring fluorine-containing compound was fluoroacetate (Figure 1.2 a) in 1943 from African plant *Dichapetalum cymosum*, but later on was found in some South American and Australian plants.

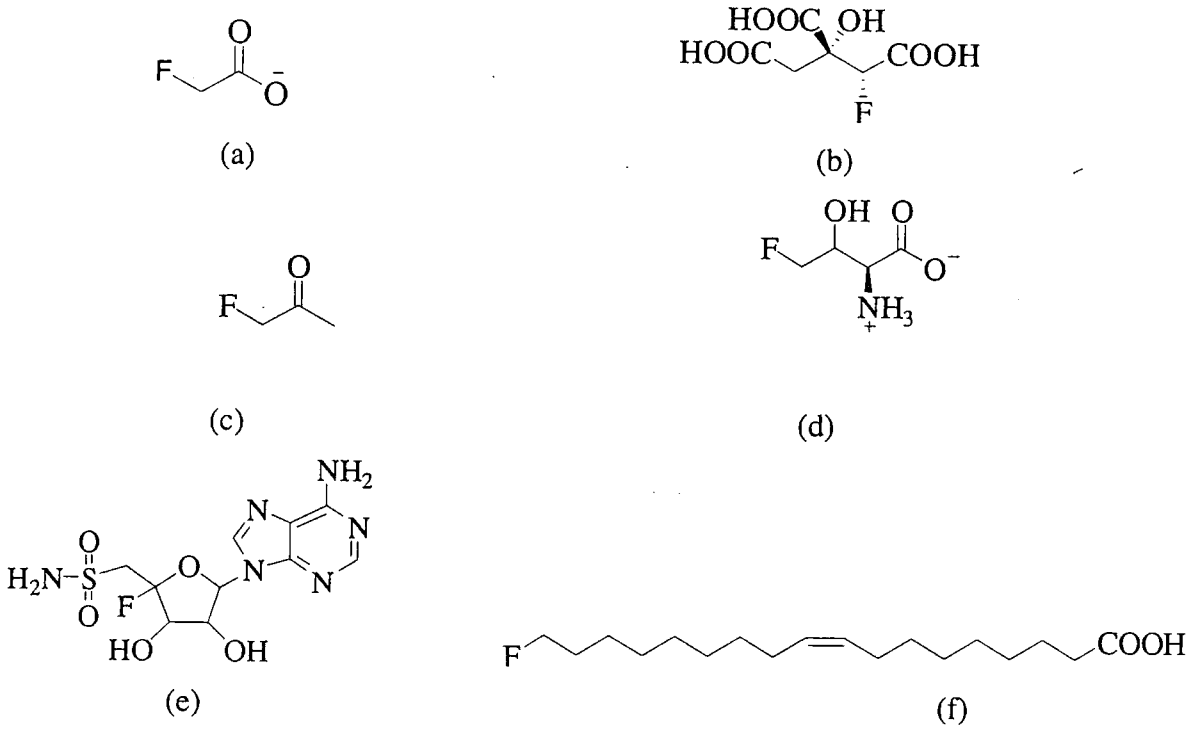


Figure 1.2

Till now, only 13 naturally occurring compounds containing fluorine have been identified, 8 of them being ω-fluorinated long chain fatty acids (Figure 1.2 f).[3] The toxicity of the fluoroacetate is considered to originate from (2R, 3R)-fluorocitrate (Figure 1.2 b) in which it is converted *in vivo* by the enzyme citrate synthetase. Consequently, many plants which contain fluoroacetate contain fluorocytrate as well. Fluoroacetone (Figure 1.2. c) is identified as natural product in the late 1960's, but its identification is regarded as insecure. This compound was trapped as the hydrazone derivative and identified according to the retention time on paper chromatography. Recent studies imply this compound is actually

fluoroacetaldehyde, which was believed to be highly unstable and therefore inprobable. Nucleocidin (Figure 1.2.e), isolated from an organism *Streptomyces calvus,* has a wide range of antibacterial activity, but it has been shown to be toxic for clinical use. 4-Fluorothreonine (Figure 1.2.b) is isolated from *S. Cattleya* and investigation on its biosynthesis is currently underway by O'Hagan and co-workers.

1.4 Properties of fluorine as an atom and as a substituent

Fluorine is the first and smallest element in the Periodic table with *p* orbitals which can achieve a noble gas electron configuration by receiving just one additional electron. This is causing many unique properties of fluorine as an atom and as a substituent in molecules (Table 1.1).

Table 1.1 Physical properties of hydrogen and halogens[4, 5]

	H	F	Cl	Br	I
Electronegativity	2.20	3.98	3.16	2.96	2.66
Ionis. Energy (kJ/mol)	1312	1681	1251	1137	1010
Electron affinity (kJ/mol)	74.0	332.6	349.2	304.3	295.8
Van der Waals radius (Å)	1.20	1.47	1.75	1.85	1.98
Bond energy C-X (kJ/mol)	446.4	546.0	305.0	290.3	231.7
Bond length C-X (Å)	1.09	1.31	1.76	1.93	2.14

Electronegativity. Fluorine is the most electronegative element with a value of 3.98 on the Pauling scale (Table 1.1). This may be the origin of many modifications of properties of molecules with fluorine as a substituent in comparison to non-fluorinated analogues. When fluorine is introduced into an organic molecule, the electronic distribution can be changed and therefore the dipole moment of the molecule, reactivity, stability, acidity and basicity of the other functional groups may also be altered.

With the introduction of fluorine, ***acidity*** is usually increased with exception of planar conjugate anions, for which the result is often unpredictable.[6] ***Basicity*** is usually reduced as the number of fluorine atoms increase in a molecule. This is of great importance

in medicinal chemistry (drug delivery), where the presence of highly basic groups can have a limiting effect on bioavailability due to the decrease in the membrane permittivity of the compound.

According to Pauling and Berstein, ***the strength of hydrogen bonding*** depends on the electronegativity of the proton acceptor and the atom covalently bonded to the hydrogen bonding. Since fluorine is the most electronegative element, it should act as a strong proton acceptor and make a strong hydrogen bond. In the case of the fluorine anion (F^----H) and hydrogen bifluoride anion (F-H-F^----H), the hydrogen bond is considered as one of the strongest hydrogen bonds.[7] However, in the case of organofluorine compounds the situation is different, fluorine from the C-F bond behaves as a very weak proton acceptor so there is some discussion[8, 9] whether fluorine in C-F is forming hydrogen bonds at all (<4 kcal mol^{-1}, >2.2 Å). This exceptional behaviour of halogens and fluorine particularly, in comparison to nitrogen and oxygen, which readily form hydrogen bonds, is not completely understood. A possible reason is that strength of the hydrogen bonds does not depend on the electronegativity of the proton acceptor, since electronegativity is a measure of the ability to attract shared electrons not protons (although most of the good proton acceptors are actually electronegative). Furthermore, the reason for low proton affinity could be a fact that fluorine is a 'hard atom', with low basicity and low-lying lone electron pair orbitals. According to Dunitz,[9] these bonds are so rare and weak that is more matter of taste to say hydrogen bond or polar-polar interaction.

Size of the fluorine atom. Fluorine is a small atom with Van der Waals radius: 1.47 Å. According to many authors, fluorine can be considered as a bioisosteric replacement for hydrogen,[10] so its compounds are thought to be sufficiently similar in size and shape to their non fluorinated analogues. Nevertheless, fluorine is actually more similar to oxygen (1.52 Å).[11, 12] The size of a trifluoromethyl group (r_v (CF_3) =2.2 Å) is actually sterically literally the same size as an isopropyl group (r_v ($CH(CH_3)_2$)=2.2 Å). Also, methoxybenzene without any substituent at the ortho-position adopts a planar conformation, while none of the crystal structures of trifluoroanisole, that are found in Cambridge Structural Database, have CF_3 in the plane of the ring.[9] Despite this, often the substitution of a single hydrogen for a fluorine causes minimal steric disruption.[13] For example, fluoroacetyl-CoA is used as an excellent acetyl-CoA mimic for citrate and malate

synthesis. Consequently, the steric effects of introducing a fluorine atom into a molecule are often unpredictable.

Electron affinity is often considered as an anomalous property of fluorine, since it is slightly lower than chlorine, but higher than bromine and iodine (Table 1.1). Politzer[14] has shown at a plot between the electron affinities and ionization potential of the halogens that fluorine has a lower electron affinity than chlorine. The discrepancy was 110 kJ mol^{-1} lower than expected according to the linear extrapolation from chlorine, bromine and iodine. The possible reason for the "anomalous property" of fluorine is thought to be repulsion between unshared electrons in the relatively small electron shell. However, in comparison to the elements from the first row of the periodic table such as nitrogen and oxygen, electron affinity of fluorine appears consistent.[15]

Ionization energy. Fluorine has higher ionization energy (1681 kJ mol^{-1}) than any other element apart from helium and neon. This is probably the reason why F^+ species have not yet been observed.

Length and strength of the C-F bond. Fluorine forms the strongest and shortest single bond to carbon (Table 1.1) of all the halogens. As the number of fluorine atoms in a molecule increases, the length of the bonds gets shorter and stronger, which is a unique properties of the halogens.

In conclusion, fluorinated organic compounds often possess unusual physical and chemical properties and consequently, they have found wide applications ranging from pharmaceuticals to material science.

1.5 Applications of fluorinated compounds

The increased strength of the carbon-fluorine bond over a carbon-hydrogen bond enables the synthesis of various compounds and materials with high thermal and chemical stability. These compounds have found wide applications as lubricants (Figure 1.3 a), coatings, refrigerants, aerosols, and foam blowing agents. Starting with manufacturing of Teflon® (poly(tetrafluoroethylene) at DuPont, various fluoro-polymers are still produced on a large scale (Figure 1.3 b).

$-(OCF_2CF_2CF_2)_n-$

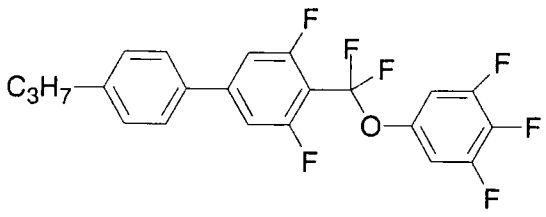
(a) Demnum®, Daikin

Lubricant

$-CH_2CF(OCF_2)_nCFCF_2-$

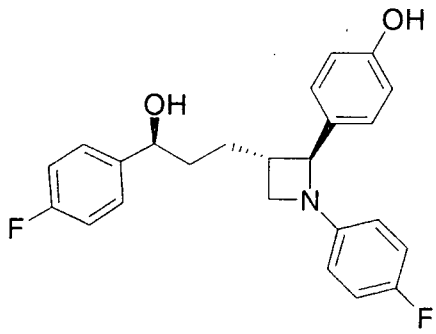
(b) Cytop®, Asahi Glass Co.

Computer chip manufacture



(c) Liquid crystal

Matrix for LCD



(d) Ezetimibe

Modulator of cholesterol mechanism

Figure 1.3

Trifluoromethylphenyl groups incorporated into azo, anthraquinone and triphenylmethane dyes have been claimed to improve the brightness, tinctorial values and lightfastness.[16] Fluorinated liquid crystals (Figure 1.3 c) have found applications in active matrix LCD technology. Fluorine substituents in liquid crystals help to decrease melting point, improve solubility, but also alter the polarity in the molecule to give desirable optoelectronic properties.

A benzotrifluoride group is often part of the structure of many plant protection agents. This moiety is also often incorporated in many pharmaceuticals since CF_3 group is known to increase lipophilicity, accelerate adsorption and distribution within an organism. Development of new drugs for the pharmaceutical industry has led to impressive progress in the total synthesis of complex molecules (Figure 1.3 d). According to the World drug Index, there were 31 new compounds approved in 2002, nine of them contain fluorine.[8]

Organofluorine compounds are relatively new and their ecological impact on global environment was difficult to predict. For example, whether due to their high stability that does not allow their degradation like other pollutants or strong infrared absorption bands, chlorofluorocarbons (CFC) are suspected to be the cause of the ozone layer depletion and green house effect. Many CFCs gained huge importance in daily life and intense research activity were initiated for their replacement to more rapidly degradable alternative compounds (HFC).

1.6 Methods for the formation of carbon-fluorine bonds

As organofluorine compounds are rarely found in nature, consequently the majority of fluorinated compounds are man-made. Due to the huge demand for their production, many methods have been developed for this purpose. They can be placed into in two categories:

- Methods for producing perfluorinated and polyfluorinated compounds, which include fluorination with metal fluorides, electrochemical fluorination and perfluorination with elemental fluorine.

- Selective fluorination of organic compounds, which can be roughly categorized according to their mechanism of fluorine introduction in the molecule:

- Addition to unsaturated compounds

- *HF addition.* Anhydrous hydrogen fluoride adds to double and triple bonds in the presence of catalyst (TaF_6, AlF_3, WF_3, $MoCl_3$, BF_3).[6]
- *fluorine addition.* Successful addition of fluorine to unsaturated bond of various organic compounds have been achieved by using elemental fluorine, XeF_2, CF_3OF, $ArIF_2$, $CsSo_4F$.
- *halofluorination.* Halogenfluorides (chlorine fluoride, chlorine trifluorides and iodine and bromine fluorides) can be generated *in situ* and be used for halogen fluorination of olefins. This can usually be accomplished using a source of positive halogen and a fluoride ion donor.[17-20]

- Nucleophilic reagents, which replace:

- *halogen by fluoride ions.* In a great number of classes of organic compounds, such as sulfonyl acetyl halides, alkyl halides, mono-and perhalogenated benzenes and heterocycles, the halogen atoms can be replaced by fluoride ion. The most commonly used reagents are AgF[21], KF[22-24], CsF[25]).
- *hydroxyl group by fluorine.* This method involves introducing fluorine into organic compounds by the replacement of the hydroxyl group in alcochols, hydroxyl compounds and carboxylic acids. (DAST, Olah's reagent).

- Electrophilic reagents which replace hydrogen with fluorine:

- *elemental fluorine* (in polar solvents)
- *N-F reagents* (Selectfluor, Accufluor)
- *O-F reagents*
- XeF_2

The aim of this thesis is to develop methods for selective electrophilic fluorination, so this review of literature particularly focuses on the most important and recent advances of reagents in this area. Nucleophilic fluorination[26-28] and fluorination by addition to unsaturated compounds[6, 29, 30] have extensively been reviewed in the literature and the reader can be directed to that literature and to the references cited therein.

1.7 Electrophilic reagents

1.7.1 Elemental fluorine

Fluorine at room temperature exists as a diatomic molecule F_2, a pale yellow gas. It condenses at −188°C to a yellowish orange liquid and solidifies at −220°C to a yellow solid. Very low bond dissociation energy makes fluorine the most reactive element, which reacts with most organic and inorganic compounds. Although in nature, fluorine occurs as only one isotope, ^{19}F, with atomic weight 18.9984, isotopes with atomic weight between 17 and 22 can be artificially prepared. The longest half life isotope ^{18}F (110 min) incorporated in the organic molecules has found applications as a mechanistic probe for PET diagnostics.[31]

Due to its strong odor, it is easy to detect fluorine gas at 20 ppb. Since it is known as extremely corrosive and irritating to the eyes, skin, and respiratory tract, the American Conference of the Governmental Industrial Hygienist (ACGIH) have suggested an emergency exposure limit of 150 ppm for 10 min. Comprehensive studies determined a rat lethal concentration value (LC_{50}) of 3500 ppm for a single 5 min exposure.[16]

1.7.1.1 Production of elemental fluorine

Contemporary industrial production of fluorine is still based on Moissan's method of electrolysis of anhydrous potassium bifluoride with various concentrations of hydrofluoric acid.[32] Stainless steel cells are used also as a cathode and operate at a medium temperature range (60-110°C). The anode is a very important part of the cell and advances in design were responsible for recent improvement in productivity and length of the cells life. They are mainly made of carbon blocks by conversion of petroleum coke and pitch binder. Each 1 kilogram of the product fluorine demands 1.1 kilogram of high purity anhydrous HF.[16]

The synthesis of fluorine gas was also achieved chemically (Figure 1.4) by a displacement reaction using potassium hexafluoropermanganate and a strong Lewis acid, antimony pentafluoride.[33]

$$2KMnO_4 + 2KF + 10HF + 3H_2O_2 \xrightarrow[50\%\ \text{aqu.HF}]{74\%} 2K_2MnF_{6(s)} + 8H_2O + 3O_2$$

$$K_2MnF_{6(s)} + 2\,SbF_5 \xrightarrow[150^\circ C]{>40\%} 2\,KSbF_6 + MnF_3 + 1/2\,F_{2(gas)}$$

Figure 1.4

The largest manufacturers of fluorine gas are, Air Products and chemicals (USA), British Nuclear Fuels plc. (UK), Central Glass co., (Japan) but there are also medium and large commercial plants in Canada, Italy, France, Germany and Russian Federation (Former USSR).

1.7.1.2 Mechanism of fluorination with elemental fluorine

Formation of the C-F bond from a C-H bond using elemental fluorine as fluorinating agent can proceed by two mechanisms dependant on the temperature and solvents that are employed. Transformation can occur via electrophilic and radical pathways.

1.7.1.3 Electrophilic fluorination

Fluorination of organic compounds can proceed selectively in media containing Lewis acids, protic acids and solvents with high dielectric constants, but substrates that contain electron-rich sites are required.

Rozen[34] demonstrated in the reactions between fluorine and saturated hydrocarbons that selective substitution proceeds at tertiary C-H with retention of configuration. The following mechanism was suggested (Figure 1.5):

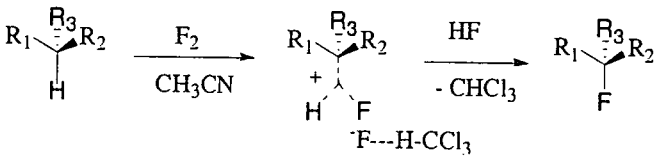


Figure 1.5

This mechanism involves a 3 center 2 electron bond pentacoordinate intermediate which collapses and leads to the formation of the C-F bond.

Chambers[35] remarked on the importance of high acidity and permittivity of the solvents for successful fluorination (Table 1.2) with the conclusion that permittivity is a more important factor.

Table 1.2 Acidity and relative permittivity of some solvents

Solvent	pKa	ε_r (20°C)
H_2SO_4	-3.6	100
HF	3.2	
HCOOH	3.8	58.5
CH_3CN	25	35.9

This does not apply for all cases, for example nitromethane (CH_3NO_2) was shown to be a poor medium although it has similar permittivity to acetonitrile, which was shown to be the best medium for fluorination of hydrocarbons. It was suggested that acetonitrile reacts with fluorine and forms an N-F reagent *in situ* (Figure 1.6), but no evidence in the ^{19}F NMR spectrum for its formation was observed.

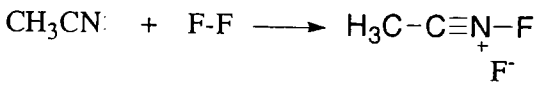


Figure 1.6

Although there has been some discussion concerning whether reaction proceeds via an electrophilic or radical mechanism, most of the arguments are in favor of an electrophilic process when the substrate possess an electron rich site. Fluorine is, at room temperature, less than 1% dissociated. In the majority of the reported studies, the reactions were performed at 0°C or lower temperature, so concentration of the dissociated fluorine should not be enough to initiate the radical chain process. Furthermore, polar solvents such as $CHCl_3$, CH_3CN are good radical scavengers. This kind of reaction medium acts as an F^- acceptor and an ionic type of reaction is favored. Also, in comparison to the other electrophilic reagents such as Selectfluor™, the reaction with elemental fluorine results in the same products.[36]

A theoretical study of the mechanism of selective fluorination of saturated hydrocarbons by molecular fluorine was reported by Morokuma and Fukaya recently.[37] Particular attention was stressed on the participation of the solvent molecules $CHCl_3$ in the process and it is compared to the case without intervention of any solvent molecule. They studied two substrates, methane (CH_4) and isobutane (t-Bu-H). In the reaction CH_4+ F_2, the overall barrier is too high to proceed as an electrophilic process even with taking the addition of $CHCl_3$ into consideration, so in this case it is more likely that a radical process proceeds. In the case for isobutane (t-BuH), the rate determining barrier is lower than for the methane due to the electron-donation of the CH_3 groups. Furthermore, with assistance of the solvent molecules, substitution at the tertiary C-H site proceeds via an electrophilic mechanism in mild conditions. The barrier in this case is sufficiently lowered (11.3 kcal mol^{-1}) to prevent radical reaction proceeding (-2.8 kcal mol^{-1} of the intermediate barrier).

The electrophilic aromatic substitution with molecular fluorine has been reported in many studies.[38-41] Two mechanisms[42, 43] were suggested involving single electron transfer (radical) and two (S_N2) electron transfers.

A radical pathway is most likely due to the remarkably low dissociation energy of F_2 (Figure 1.7).

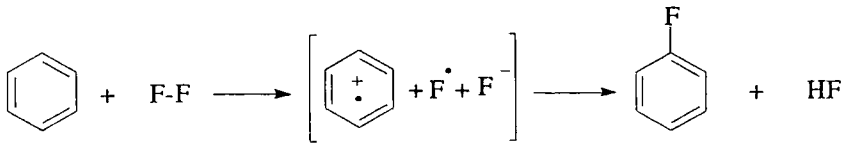


Figure 1.7

Another pathway involved nucleophilic attack on the fluorine molecule (Figure 1.8).

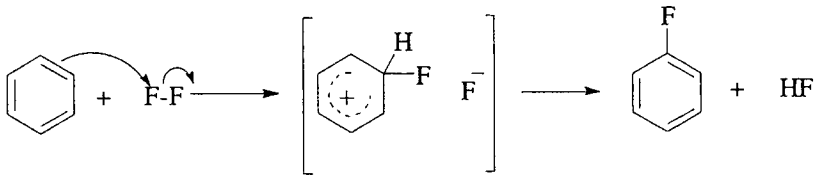


Figure 1.8

There was evidence that both mechanisms were employed, so the mechanism probably proceeds between these two extremes.

1.7.1.4 Radical fluorination

Radical fluorination is frequently considered to proceed via chain reactions since the energy of dissociation of diatomic fluorine molecule is very low.[6]

		ΔH/ kJ mol^{-1}
1. INITIATION:	$F_2 \rightarrow 2F^{\cdot}$	+159
2. PROPAGATION:	$RH + F^{\cdot} \rightarrow R^{\cdot} + HF$	-131
	$R^{\cdot} + F_2 \rightarrow RF + F^{\cdot}$	-314
3. TERMINATION:	$R^{\cdot} + F^{\cdot} \rightarrow RF$	-472
	$R^{\cdot} + R^{\cdot} \rightarrow RR$	-351

Figure 1.9

The termination and propagation (Figure 1.9) steps are highly exothermic, so more energy is released than is necessary in the initiation step. Therefore, carbon-carbon bond cleavage (C-C bond strength 346 kJ mol^{-1}) often occurs and the reaction is difficult to

control. However, radical fluorination reactions have been used for the preparation of a wide range of perfluorinated or polyfluorinated compounds such as hydrocarbons, haloalkanes, ethers, polyethers ketones, esters, etc.[2, 4, 16, 44] Control of the process was achieved by diluting fluorine gas in nitrogen and differing concentration of fluorine as reaction proceeds.

1.7.1.5 Selective fluorination

This thesis includes fluorination of saturated systems, aldehydes and various aromatic derivatives, so the following review is particularly centered on the reported recent advances in fluorination of such systems.

Fluorination of **saturated compounds** is possible in reasonable selectivity if fluorine is induced to react in an ionic mode by using polar or acidic solvents. Moreover, the substrate needs to contain an electron rich site, such as a tertiary carbon-hydrogen bond site with electron-donating substituents, to react selectively with elemental fluorine.

Rozen[34] was first to demonstrate selective fluorination of hydrocarbons, such as protected methycyclohexanol and adamantanes, using a mixture of $CHCl_3/CFCl_3$ as solvent. $CFCl_3$ is not available anymore, because it is banned by the Montreal protocol due to suspicion of its involvement in the depletion of the ozone layer. However, the importance of this work still remains, since he has advanced understanding of the mechanism of fluorination with elemental fluorine in polar solvents (Section 1.7.1.3). Rozen demonstrated also the possibility of fluorination of more complex hydrocarbons such as steroids.[45]

Successful fluorination of cyclic alkanes was reported by Chambers and Sandford (Figure 1.10).[46]

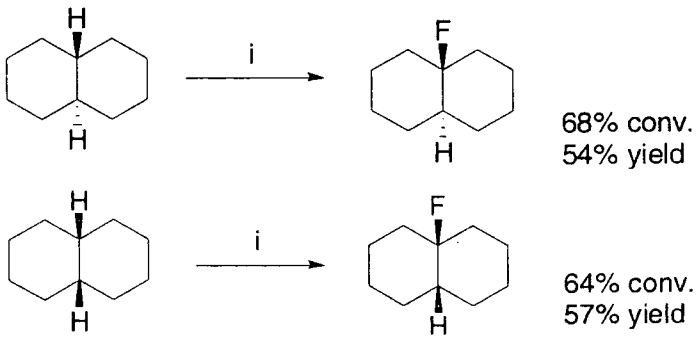


Figure 1.10 i: 10% F_2/N_2 CH_3CN, 0°C, 18 h.

The reaction resulted in retention of configuration using both *cis*- and *trans*-decalin, and proceeds probably via a three-centre two electron intermediate as suggested by Barton and Rozen.[34]

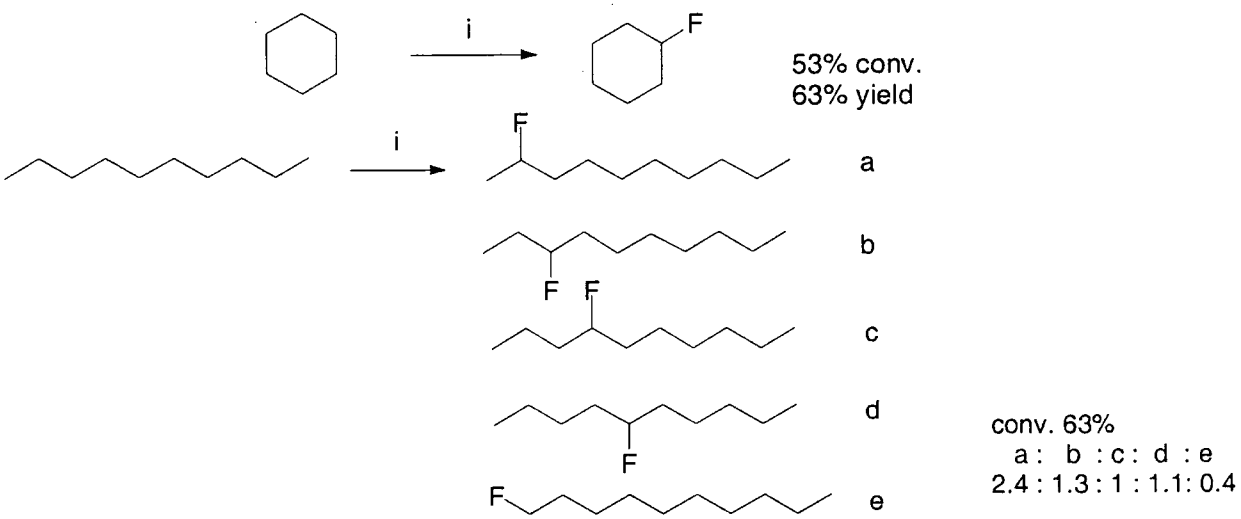


Figure 1.11 i: 10% F_2/N_2, CH_3CN, 0°C.

Reasonable selectivity was obtained in the reaction with cyclohexane (Figure 1.11) where all sites are equal, while the reaction with molecules without any dominant electron rich site such as *n*-decane, resulted in a mixture of products.

Sekiya[47] has reported fluorination of polyfluorinated etheric substrates (Figure 1.12) adsorbed on porous aluminium-trifluoride (PAF).

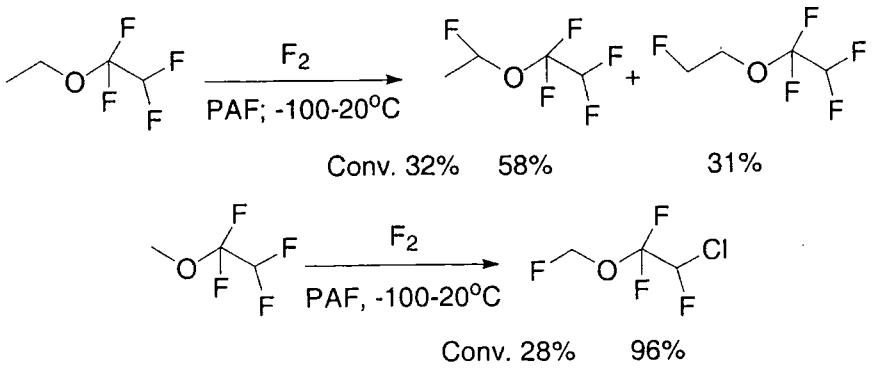


Figure 1.12

Use of the porous aluminium fluoride (PAF) prevents C-C bond or ether bond cleavage although PAF is a strong Lewis acid. Provided explanation is based on the fact that the molecules of substrates can be easily adsorbed on the internal surface of PAF, which protects the substrate from attack by fluorine and avoids the cleavage of C-C bonds.

Since **carbonyl compounds** have found numerous applications as building blocks in organic synthesis, in the literature there are many reports about fluorination of small carbonyl molecules with a variety of fluorinating agents[48] including elemental fluorine.

Chambers[42] and coworkers have conducted extensive study with 1,3-dicarbonyl compounds which with elemental fluorine readily react to give preferentially α-fluorinated products in high conversions (Figure 1.13, Table 1.3). 1,3-Diketoesters (Table 1.3, entries 5, 6 and 7) react in slightly lower conversion but fluorination at C-H bond at the 2 position is favored.

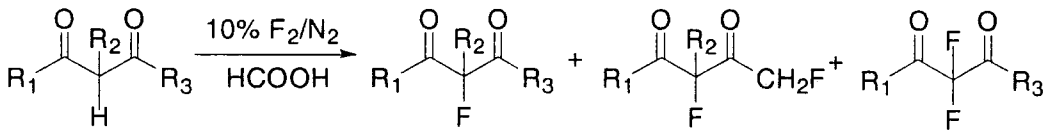


Figure 1.13

Table 1.3 Fluorination of 1,3-dicarbonyl and 1,3-diketoesters.

Entry	R_1	R_2	R_3	Yield (a) (%)	Yield (b) (%)	Yield (c) (%)	Conv. (%)
1	CH_3	H	CH_3	70	11	3	90
2	CH_3	CH_3	CH_3	76	9	-	90
3	CH_3	Cl	CH_3	65	7	-	85
4	-	$-(CH_2)_4-$	CH_3	70	10	-	95
5	C_2H_5O	H	CH_3	80	10	1	60
6	C_2H_5O	CH_3	CH_3	85	5	-	25
7	C_2H_5O	$-(CH_2)_4-$	CH_3	90	4	-	90

It was suggested that the reaction proceeds through an addition-elimination mechanism, where elemental fluorine is electrophilicly added to double bond of the enol form (Figure 1.14).

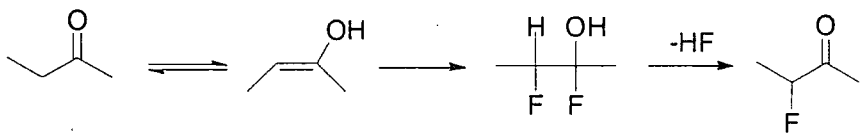


Figure 1.14

Cyclic 1,3-dienones (Table 1.3, entries 4 and 7) react more readily than acyclic analogues, since cyclic systems form enolates more readily, which react conveniently with elemental fluorine. Established relationship between structure of carbonyl compounds and reactivity towards electrophilic fluorine is as following:

cyclic 1,3-diketones > acyclic 1,3-diketones > acylic 1,3-ketoesters > acyclic 1,3-ketoacetoamides > acyclic 1,3 diesters

Most convenient solvents for direct fluorination are considered to be acetonitrile and formic acid, while Bowden[49] reported that HF/H_2O mixture gave very good results. Further improvement in the conversion was reported by Chambers using transition metal salts, in particular copper-(II) salts to catalyze the reaction.[50, 51]

Recently, Moilliet[52] reported fluorination of 1,3-ketoesters in high conversion and good selectivity, employing methanol or a mixture of methanol/water (Figure 1.15, Table 1.3).

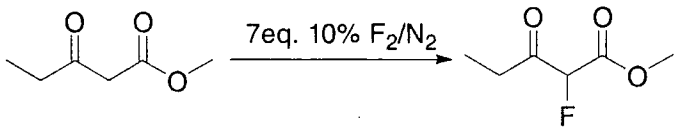


Figure 1.15

Table 1.4 Fluorination of 1,3-ketoester in different solvents.

Solvent	conv. (%)	yield (%)	tar (%)
CH_3OH	92	70	9
CH_3OH/H_2O	78	71	9
CH_3CN	56	55	23

In a recent publication, Adachi[53] demonstrated how the flow rate and concentration of fluorine affect the conversion of the reaction. Using the same substrate as Moilliet (Figure 1.15), he managed to convert completely the starting material, which is very important for industrial production since separation of the products from the starting material is very difficult. The quantity of the introduced fluorine (190ml min^{-1} → 40ml min^{-1}) has to be reduced as the reaction proceeds and the remaining amount of starting material was decreased, to avoid further reaction of the monofluorinated product.

Fluorination of **aromatic compounds** has been investigated by several researchers. Grakauskas[54] demonstrated in 1970 that fluorination using elemental fluorine proceeds by electrophilic substitution and it is similar to chlorination and bromination. Selectivity of fluorination of monosubstituted derivatives was low and substituent orientation was observed in the *meta*-position for nitrobenzene and *ortho/para*- for toluene and anisole.[38] Misaki[55] published that choice of the solvent has an influence on the distribution of the products.

In earlier work by the Durham group,[42] it was concluded that fluorination of the 1,4-disubstituted aromatic derivatives depend on the substituents X and Y (Figure 1.16). When X and Y are both activating electron-donating groups, reaction is difficult to control and resulted with polymerization and many side products. Introduction of the one electron-withdrawing group slightly deactivates the system (Table 1.5), therefore reaction proceeds with good conversion and selectivity.

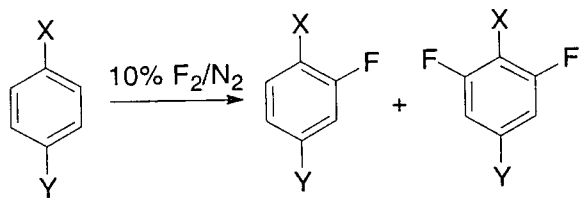


Figure 1.16 (a) (b)

Table 1.5 Fluorination of 1, 4-disubstituted benzene derivatives

Entry	X	Y	Solvent	Temperature	Conv.(%)	a (%)	b (%)
1	NHAc	OCH_3	HCOOH	10	mixture		
2	CHO	CH_3	H_2SO_4	10	74	60	-
3	OCH_3	NO_2	HCOOH	10	100	50	19
4	CH_3	NO_2	HCOOH	10	75	81	2
5	Cl	NO_2	HCOOH	10	47	44	trace
6	OH	CN	HCOOH	10	84	64	10

Although, fluorine can be an oxidizing reagent, fluorination proceeds exclusively at the ring without transformation of the carbonyl group (Table 1.5, entry 2).

Moilliet[56] and coworkers published study of fluorination using elemental fluorine of the 1,4-substituted fluorobenzene derivatives resulting in excellent conversion and selectivity (Figure 1.17).

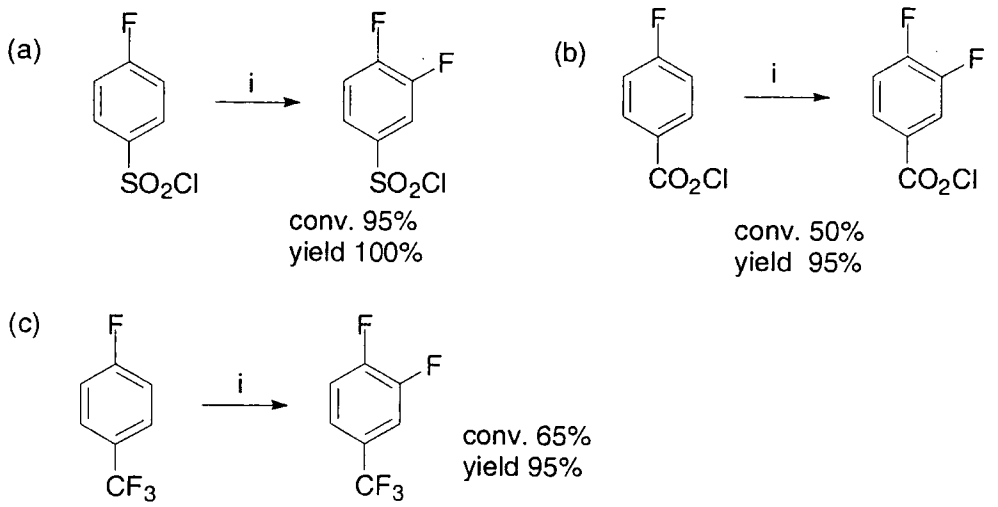


Figure 1.17 i= 2eq. 10% F_2/N_2; -30°C; MeCN.

Later, Moilliet[57] achieved efficient fluorination (Figure 1.18) of various tri-substituted benzaldehydes (vanillin, vanillic acid, veratraldehyde, etc.) in sulfuric acid as a solvent.

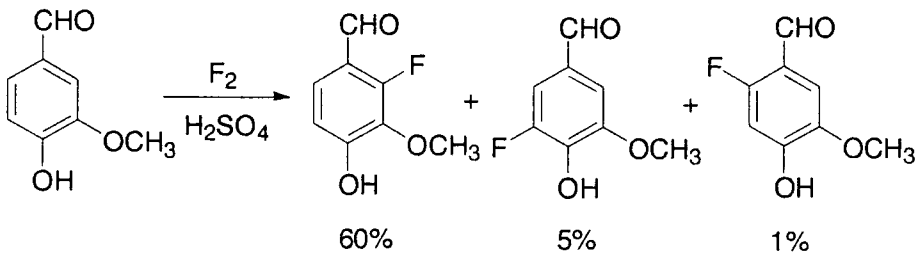
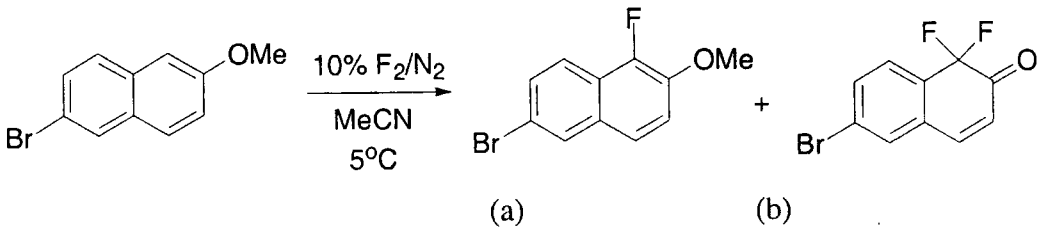


Figure 1.18

High selectivity of the reaction was explained due to protonation of carbonyl causing a positive charge on this carbon and together with association with the oxygen at the 3-position, holds the polarized molecule of fluorine close to the position 2. Therefore, the reaction took place at 2-position, although it is relatively crowded at neighboring positions.

Direct fluorinations of fused ring systems such as naphthalene, anthracene, phenathrene and pyrene (Figure 1.19) were reported by Greenhall.[58]



(a) (b)

Figure 1.19

After 80 min, bromomethoxynaphthalene was converted (37%) into the monofluorinated product (Figure 1.19 a). When additional amount of elemental fluorine was passed through the solution, conversion was determined to be 81%, but with a considerable amount of difluorinated product present (Figure 1.19 b).

Chikaral has reported fluorinated of L-DOPA derivatives using isotope $^{[18]}F_2$ [59, 60]. In a recently published study[59] he published a successful one pot nitration and fluorination of L-tyrosine in TFA and HF solvent (Figure 1.20).

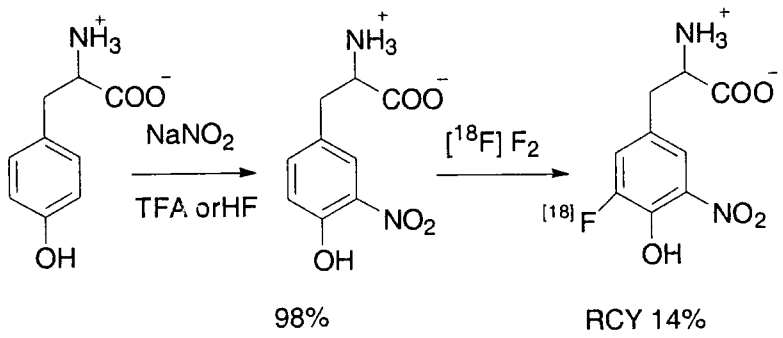


Figure 1.20

In this publication they observed radiochemical yields of fluoronitrotyrosine[59] are lower than fluorination of L-tyrosine (30%). The electron-withdrawing nitro group renders the aromatic ring less susceptible to electrophilic substitution, which they proved in competition experiments.[61]

Chambers and Sandford[62] reported that fluorination of quinoline (Figure 1.21) yielded in mainly substitution at the 5- and 8-positions, as expected for an electrophilic process.

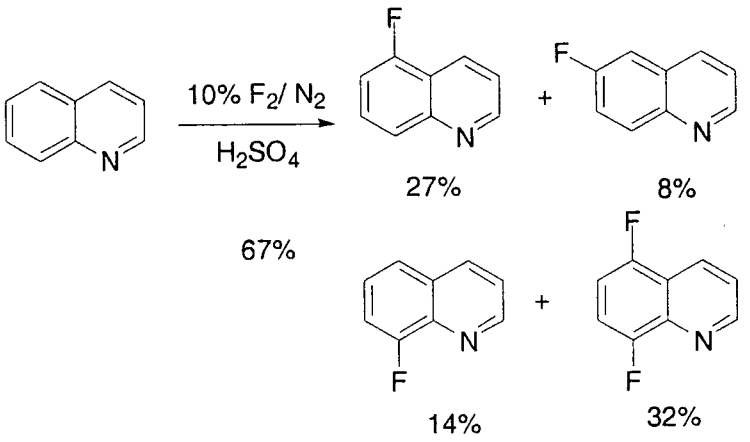


Figure 1.21

Introduction of substituents at appropriate positions provides higher selectivity and makes this methodology efficient for synthesis of a range of fluorinated substituted heterocycles (Figure 1.22).

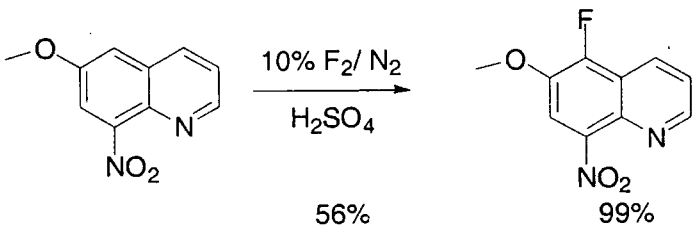


Figure 1.22

Elemental fluorine can be used for performing reactions other than fluorination, such as iodination, bromination, oxidation, amidation etc. It was pointed out that fluorine reacted with bromine to give an interhalogen compound (Figure 1.23).[63, 64]

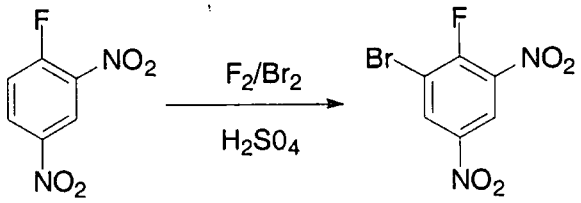


Figure 1.23

Interhalogen compound is powerful source of bromonium ion, which is capable of reacting with very deactivated systems.

1.8 Electrophilic "N-F" Reagents

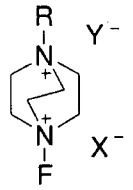
Although elemental fluorine can be used as a suitable reagent for industrial production of fluorinated compounds, the difficulties associated with safety, corrosive properties and sometimes lack of selectivity were the impetus for the development of alternative electrophilic fluorinating agents which can be used also as standard laboratory reagents.

The potential of N-F compounds as fluorinating reagents was noticed almost 40 years ago,[65] however, just in the last two decades, N-F reagents have received a great deal of attention. Their development has afforded a versatile range of fluorinating agents and mediators for other reactions, such as oxidation, halogenations and introduction of alkoxy, amido, azido, nitro-group, etc. N-F compounds can be divided into two groups of reagents:

- Neutral compounds (R_2NF) such as N-fluoro-sulfonyl derivatives, N-fluoroamines and N-fluoroamides.
- Quaternary ammonium salts ($R_3N^+F\ A^-$) which are categorised as N-fluoropyridinium salts and saturated derivatives.

The class of neutral reagents are usually prepared by direct fluorination using elemental fluorine or electrochemical fluorination using anhydrous hydrofluoric acid, while all of the quaternary salts are prepared using dilute or neat elemental fluorine.

The discovery of the saturated derivatives of quaternary ammonium salts arose from the joint research of Banks and co-workers (UMIST, UK) and Air-products and chemicals (Pennsylvania, USA). They synthesised a whole range of N-F triethylenediamine systems (Figure 1.24):



X, Y=-BF_4, -PF_6 and -OTf, R=-CH_3, -C_2H_5, -C_8H_{17}, -$ClCH_2$, - CH_2CF_3, -OH

Figure 1.24

The fluorinating power of these derivatives is amplified with an increase in electron-withdrawing capability of the substituent R.

There are several commercially available "N-F" reagents including 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-octane bis(tetrafluoroborate) (Selectfluor™, Air products), 1-hydroxy-4-fluoro-1,4-diazoniabicyclo-octane bis(tetrafluoroborate) (Accufluor™), N,N'-difluorobipyridinium tetrafluoroborate and derivatives (Mec, Daikin). [66-76] The following sections summarised the use of these reagents, with particular attention being given to Selectfluor™.

1.8.1 Mechanism of fluorination

Differding has reported several studies concerning the mechanism of fluorination using N-F reagents,[77-79] proposing two different mechanisms. According to one proposition, **nucleophilic attack** of an electron-rich centre of the organic molecule on the electron-deficient nitrogen-fluorine bond results in fluorine transfer.

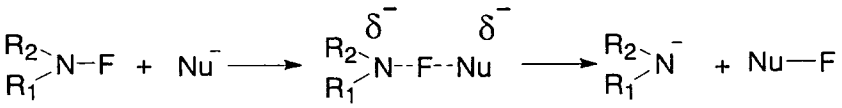


Figure 1.25

As shown on the Figure 1.25, this is an S_N2 type reaction mechanism with elimination of R_2N^-, as an effective leaving group.

Single electron transfer (SET) proceeds through the formation of a charge transfer complex of the nucleophile and an electron-deficient molecule of Selectfluor™ (Figure 1.26).

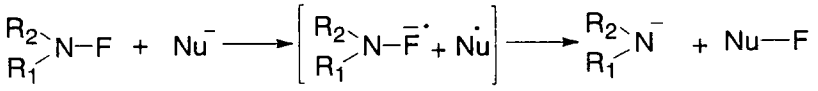


Figure 1.26

There is evidence for both mechanisms but a radical-clock-type experiments with nucleophiles rule out a radical mechanism.[77] A detailed discussion of the possible mechanisms was presented in a review of electrophilic N-F fluorinating reagents by Pez.[80]

1.8.2 Selectfluor™

1.8.2.1 Production of Selectfluor™

Selectfluor™ is a white non hygroscopic solid salt with high melting point (190°C). This dicationic salt is moderately soluble in acetonitrile and alcohols and has excellent solubility in water. High positive reduction potential (E=0.33 V) predicts that Selectfluor™ will be a reactive fluorinating agent. Bulk quantities should be stored in a cool dry place and should not be heated above 90°C.

Industrial scale synthesis of Selectfluor™ was achieved and involves three steps (Figure 1.27): the chloromethylation of TEDA (i), anion metathesis (ii) and fluorination with elemental fluorine (iii).

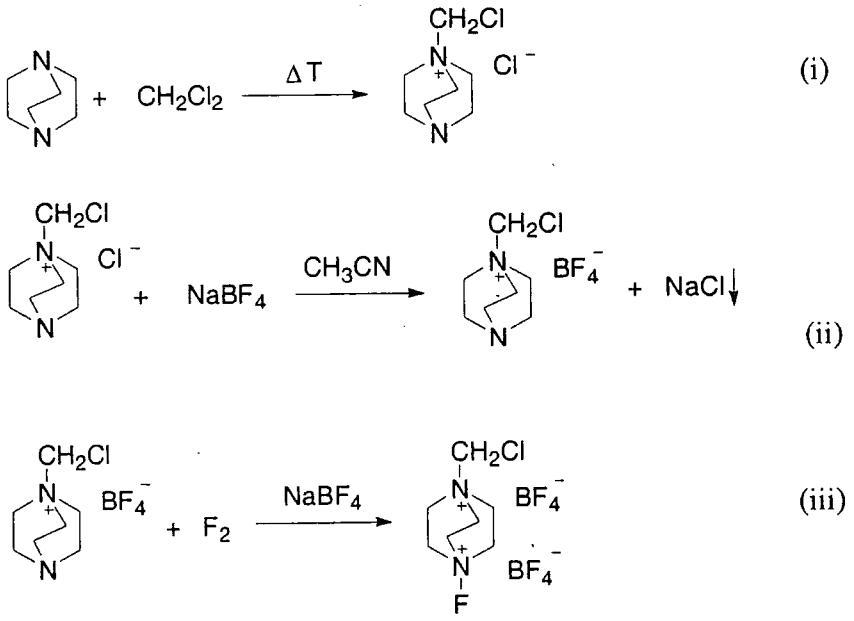


Figure 1.27

The commercial process demands efficient maintenance of low temperatures during the exothermic fluorination step [Figure 1.25 (iii)] and results in excellent yields and selectivities .[81]

1.8.3.2 Fluorination with Selectfluor™

This section presents a selection of the most recent and relevant reports on the transformation of C-H bonds to C-F bonds of hydrocarbons, carbonyl compounds, benzene derivatives and heteroaromatic compounds using Selectfluor™. Fluorination of benzene derivatives, nucleosides, steroids and carbonyl derivatives up until 1998 using Selectfluor™ has been reviewed by several authors [66, 71] and the efficiency and simplicity of its use on the laboratory scale has been demonstrated. Solvents that are usually used for these reactions are acetonitrile, methanol or trifluoroacetic acid.

Chambers and co-workers have shown that in the most instances, Selectfluor™ reacts in a similar manner to elemental fluorine with **hydrocarbons**, which implies similar reaction pathways for these two reagents.[36] Despite this, in the reaction of Selectfluor™ with *cis*- and *trans*-decalin, fluorination proceeds at the secondary carbon to give a mixture of two mono-fluorinated products (Figure 1.28), which are not produced in the reaction with elemental fluorine (Section 1.6.1.5).

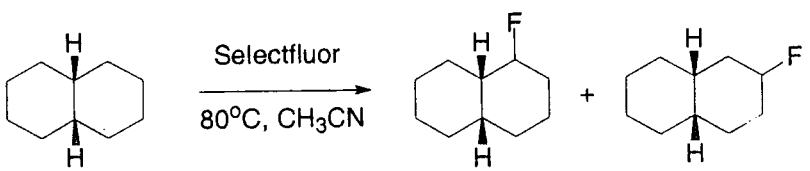


Figure 1.28

The tertiary positions are probably not approachable for the bulky Selectfluor™ molecules, so the less sterically hindered secondary positions are the more suitable reactive sites. Fluorination of adamantane occurs mainly at the tertiary site. If the reaction time was increased, hydrocarbon amides were isolated as the final products (Figure 1.29).

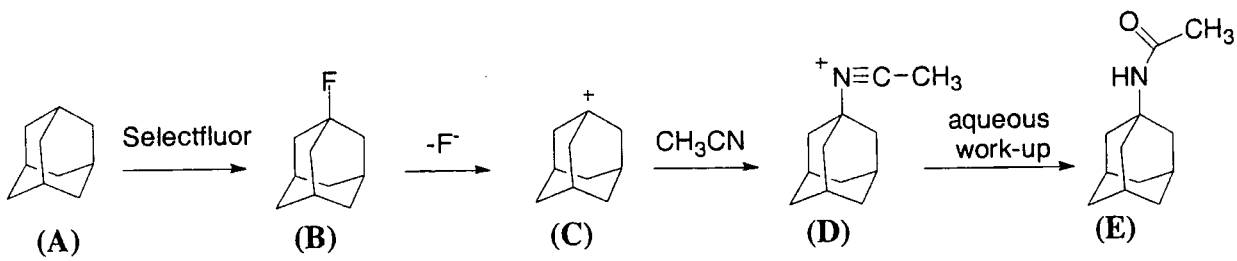


Figure 1.29

The proposed mechanism includes initial fluorination at the most electron-rich tertiary carbon, which is followed by elimination of HF. Carbocation **(C)** then reacts with a molecule of acetonitrile which is present as a solvent, giving the compound **(D)** which is subsequently hydrolysed during the aqueous work-up procedure to give amide **(E)**.

Dithio-heterocylic molecules (Figure 1.30) react readily with Selectfluor™ to give monofluorinated derivatives.[69]

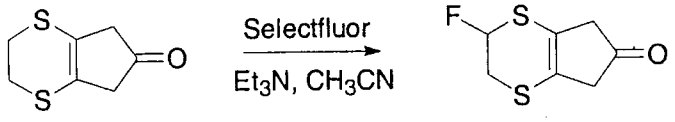


Figure 1.30

Although this molecule contains several reactive sites, such as the double bond and the α-positions to the carbonyl group, fluorination proceeds exclusively at the saturated position next to the sulphur. The possible reason for this is that the reaction proceeds through a Pummerer-like rearrangement (Figure 1.31), where initial fluorination occurs at the sulphur atom followed by elimination of hydrogen fluoride and addition of a fluoride anion.

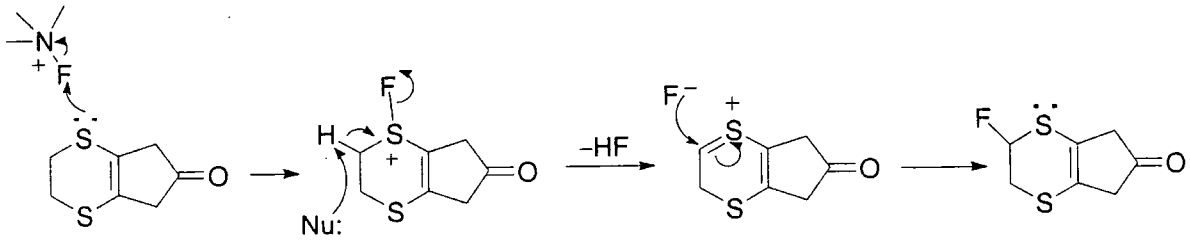


Figure 1.31

Fluorination of **alkenes** was reported by Zupan and Stavber.[76] The reaction of norbornane with Selectfluor™ resulted in the formation of two products, 2-*exo*-acetamido-7-*syn*-fluoronorbornane and 2-*exo*-acetamido-7-*anti*-fluoronorbornane (Figure 1.32) in equal amounts indicating Ritter type functionalisation. Acetonitrile is used as a solvent, but also acts as nucleophile.

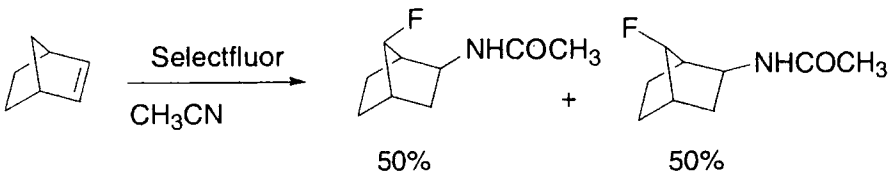


Figure 1.32

The reaction probably proceeds through a three-centre transition state (Figure 1.33) to form intermediate A, which leads to the formation of the fluorinated carbocation **(B)**.

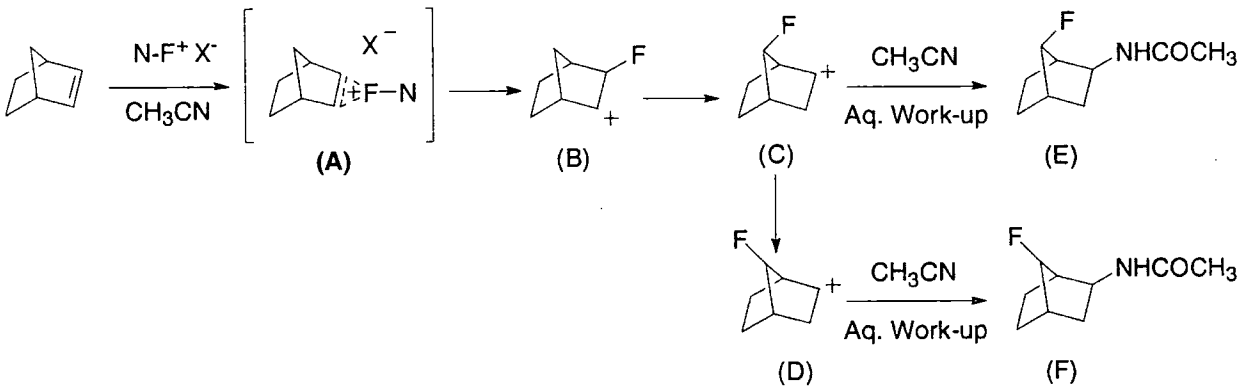


Figure 1.33

After a Wagner-Meerwein rearrangement, carbocation **(C)** reacts with acetonitrile and after aqueous work up, the final products **(E)** and **(F)** are formed.

Wong and co-workers reported effective fluorination of **2-deoxysugars** in the presence of nucleophiles (Figure 1.34).[82]

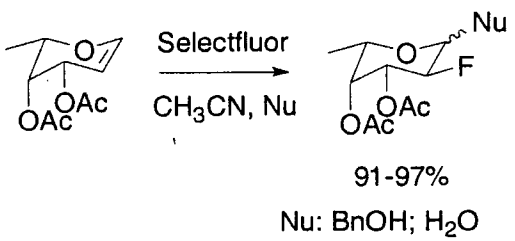


Figure 1.34

The flexibility of this methodology was demonstrated with various glycosides and a proposed mechanism (Figure 1.35) involves an oxonium intermediate which readily reacts with a nucleophile.

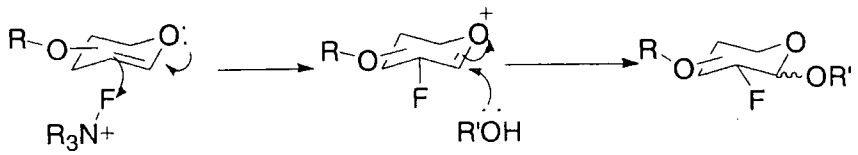
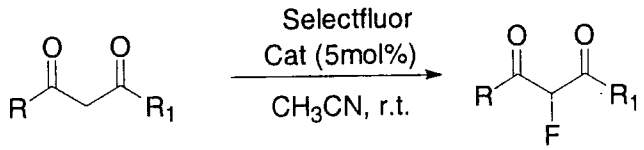


Figure 1.35

Stereoselective fluorination of organic compounds has received huge attention in the last decade. In the presence of titanium-based Lewis acid catalysts, fluorination of β-ketoesters using Selectfluor™ was achieved, resulting in good enatioselectivity (Figure 1.36).



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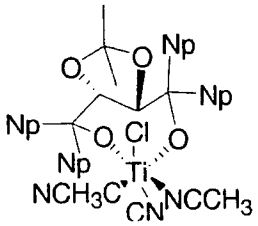


R	R_1	ee%
CH_3CH_2CO	$COCPh_2$	81%
PhCO	$COCPh_2$	81%

Figure 1.36

Current mechanisms propose that the titanium Lewis acid coordinates to the oxygen of the carbonyl groups to provide a more reactive species, similar to the enolate form.

Aromatic compounds bearing electron-releasing groups react with Selectfluor™ under mild condition in acetonitrile, with the regioselectivity depending on the position of the directing substituents.[67] This methodology was used by Kauffman and Kobarfard (Figure 1.37) in the synthesis of the two fluorinated analogues of anti-tuberculosis agents, thioacetazone and *4*-amino-salicylic acid.[83]

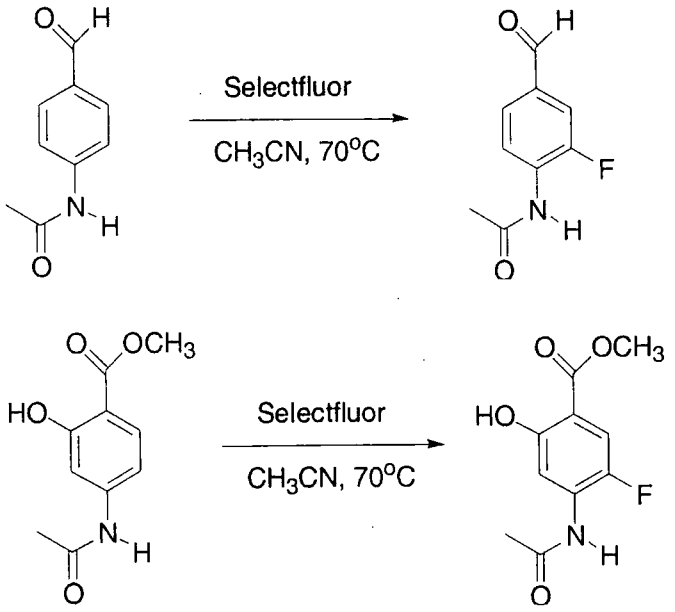


Figure 1.37

Fluorination of toluene, xylene and anisole derivatives was also achieved using ionic liquids as reaction medium, giving results that are comparable to those when acetonitrile or trifluoroacetic acid were used as solvent.[84] The process did not involve any aqueous work-up, the ionic liquids can be recycled and reused, presenting advantages in context of green chemistry. Furthermore, the fluorination cycle can be repeated to a give higher yield.

Stavber reported the efficient synthesis of cyclohexa-2,5-dienone derivatives from alkyl-phenols (Figure 1.38).[73]

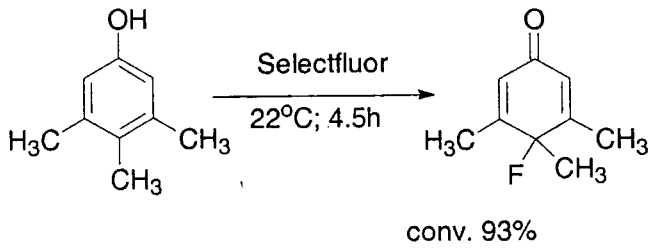


Figure 1.38

Selectfluor™ was used for the synthesis of N-fluoro ammonium salts of the cinchona alkaloids which can be used as enantioselective fluorinating agents. Banks fluorine transfer procedure was used and complete conversion was achieved after 20 minutes.

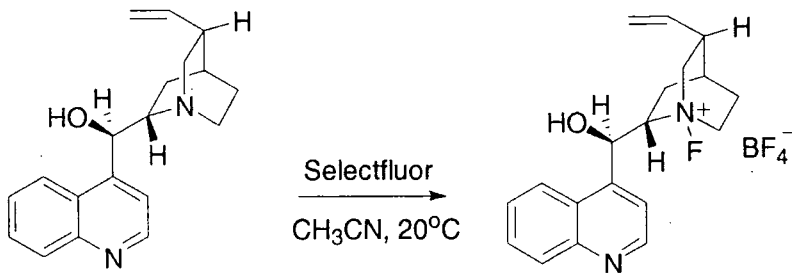


Figure 1.39

This reagent (Figure 1.39) was successfully used for the enantioselective synthesis of fluorocarbonyl compound.[85]

Efficient fluorination of heterocyclic derivatives such as indoles in ionic liquid was reported by Plaquevent.[86]

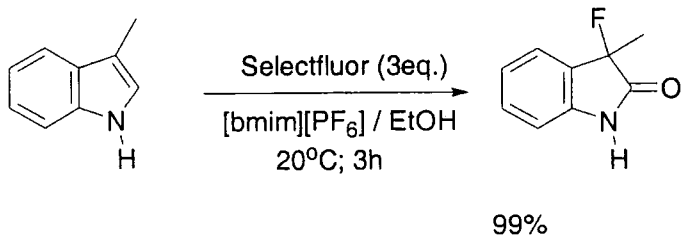


Figure 1.40

Optimum conditions were achieved by using [bmim] [PF_6] or [bmim] [BF_4] in methanol (Figure 1.40) reaching the 99% conversion.

Selectfluor™ can also be used to mediate other reactions, such as iodination, bromination[87] and a variety of transformation of functional groups. Recently, Stavber reported iodination of aryl-alkyl ketones, indonane and tetralones with elemental iodine in the presence of Selectfluor™. The regioselectivity was regulated by variation of the solvent in a similar manner to the reactions with Accufluor™ described in next Section 1.7.2.[70, 72, 88] Iodination of aromatic ethers was also accomplished with a mixture of iodine and Selectfluor™ in high conversion (Figure 1.41).

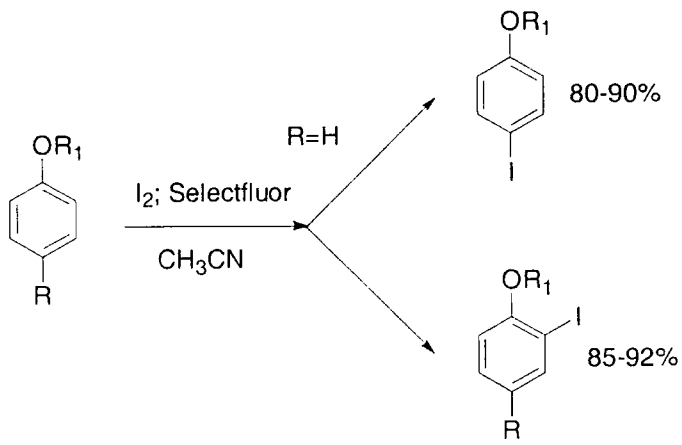


Figure 1.41 R=H, F, Cl, $COCl_3$, CHO; R_1=CH_3, CH_2Ph, Ph.

Aldehydes and ketones are successfully transformed to homolytic alcohols by allylstannanes in the presence of Selectfluor™. The efficient synthesis of the β-hydroxy thiocyanates by regioselective ring opening of epoxides with ammonium thiocyanate using Selectfluor™, as a catalyst, was also achieved, providing an approach with mild reaction conditions, short reaction times and ease handling.[89]

1.8.3 Accufluor ™

Efficient fluoro-functionalisation of organic compounds was achieved using 1-fluoro-4-hydroxy-1,4-diazoniabicyclooctane bis(tetrafluorborate), which has the commercial name Accufluor™. [66-76] Stavber reported a solvent directed fluorinaton of aryl-alkyl ketones using Accufluor™.[74] When methanol was used as solvent, fluorination proceeded at the α-carbonyl position of the alkyl group, while when acetonitrile was used, fluorination occurred at the aromatic ring (Figure 1.42). The selectivity in acetonitrile was only achieved when strongly activating groups (-NH_2, -OCH_3, -OH) were attached to the ring.

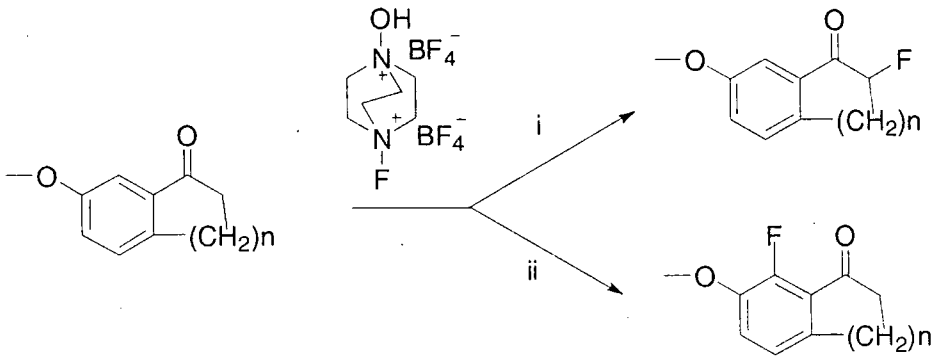
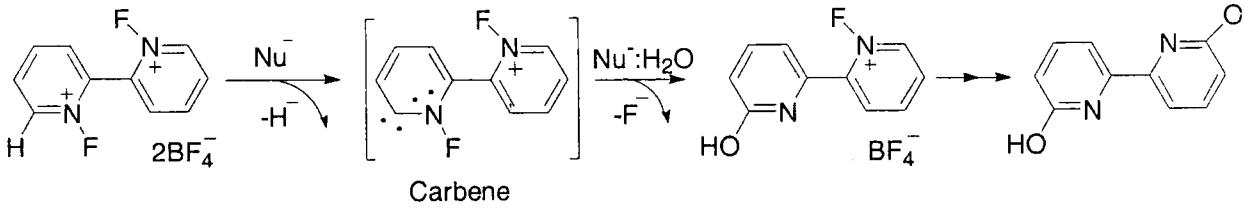


Figure 1.42 i: MeOH, 0.4-4 h. reflux; ii: MeCN, 0.5-4 h, reflux.

On the basis of the preliminary study, it was assumed that keto-enol tautomerisation was favoured in methanol, shifting the equilibrium to form more of the enol, therefore facilitating fluorination on the alkyl side of the ketone. In acetonitrile, the equilibrium is shifted favouring the keto-form, therefore the most reactive part of the molecule is the aromatic ring.

1.8.3 Pyridinium reagents (Mec ^{TM}, Daikin)

N,N'-Difluorobypyridinium tetrafluoroborate can be synthesised by the one pot reaction of 2,2'-bipyridine, with BF_3 followed by fluorination using elemental fluorine.[53] The applicability of this reagent was demonstrated with a range of substrates, such as ketones, aromatic compounds and steroids.



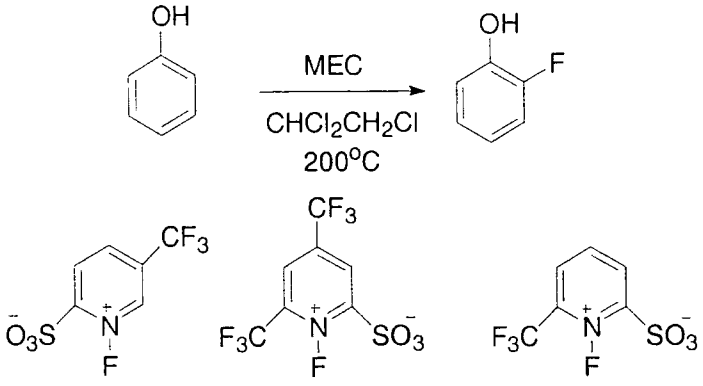
Carbene

Figure 1.43

The mechanism proceeds with adsorption of a hydrogen to generate a carbene (Figure 1.43), which then reacts with a nucleophile to give a fluorinated final product. This reagent has two active fluorines, so the process of fluorination consists of two consequent cycles. Besides having a higher effective fluorine content than Selectfluor^{TM}, a recycling

process employing simple fluorination with elemental fluorine, makes this reagent efficient and more environmentally friendly reagent.

Daikin Chemical[90] synthesised a range of pyridinuim salts, so called MEC fluorinating reagents.



a) MEC-03 b) MEC-05 c) MEC-04B

Figure 1.44

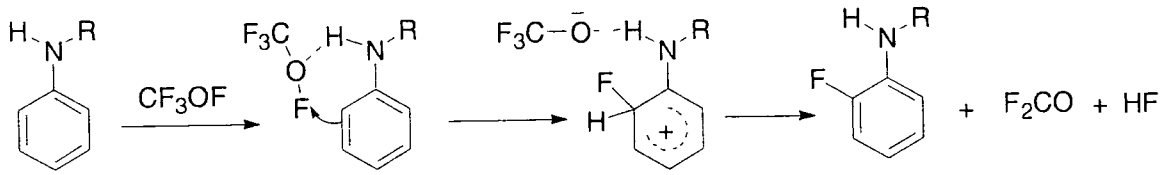
MEC-03 and MEC-04B (Figure 1.44) have the demonstrated ability to fluorinate selectively at *ortho*-position to a hydroxyl group in high conversion after 15-18 h, while reactions using MEC-05 proceeds in just 3 min with conversions 72%.

1.9 Electrophilic "O-F" reagents

This section provides an overview of electrophilic reagents containing the O-F group. In these systems their fluorinating power is not based so much on the withdrawal of electron charge from fluorine but by attaching a good leaving group to the fluorine atom. Although the use of these reagents possesses many disadvantages, their relevance to this study lies in providing us with information of possible reaction pathways and allowing us to compare efficiency of different electrophilic reagents.

1.9.1 Organic hypofluorites

Organic hypofluorites are powerful electrophilic fluorinating agents but their main disadvantage is their toxicity and tendency to react violently in contact with organic solvents. This makes them difficult to use in industrial and lab based applications. The most significant organic OF-reagents are CH_3COOF, CF_3COOF and CF_3OF which are low boiling point liquids or gases at room temperature. They are derived from their non fluorinated analogues by reaction with elemental fluorine.[91] Although a few experiments employing hypofluorites were conducted in 1959, main development in the application of these reagents was in the 1970's and 1980's, when fluorination of steroids, alkenes, enolates aromatic and heterocyclic compounds was achieve.[92-95,96]



40-60%

R: $COCH_3$; $COCF_3$; SO_2CH_3; SO_2CF_3

Figure 1.45

Successful fluorination of aniline derivatives was achieved in non-polar aprotic solvents with great preference for attack at the *ortho*-position (Figure 1.45).

1.9.2 Inorganic Hypofluorites

The most important **inorganic hypofluorite** that is used as a fluorinating agent is cesium fluoroxysulfate $CsSO_4F$. At room temperature it is a crystalline solid with the highest stability of all fluoroxy- reagents. Due to low solubility in most organic solvents, application is quite limited compared to other reagents. Selective fluorination of alkenes, alkynes and aromatic compounds has been achieved, but there are some disagreements whether the reactions proceed via an ionic or a radical mechanism.

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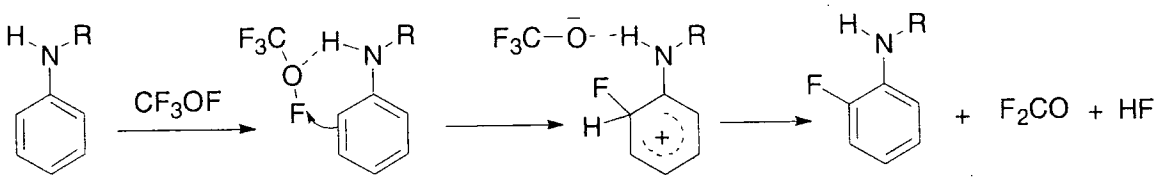

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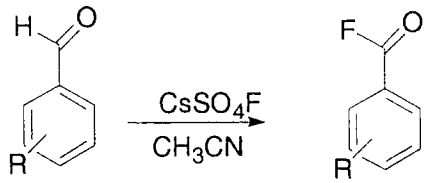
Zupan[97] and coworkers reported the oxidation of primary and secondary benzylic alcohols with $CsSO_4F$ to give aldehydes or ketones. They also conducted extensive research into the oxidation of benzaldehyde derivatives with $CsSO_4F$ (Figure 1.46).[97]



R: *4*-OCH_3; *4*-CH_3; F; *4*-CF_3; *3*-NO_2

Figure 1.46

Possible radical or electrophilic reaction pathways for fluorination using inorganic hypofluorites have been suggested. Competition experiments between benzaldehyde and its analogues were used to obtain a Hammet correlation plot. The reaction constant value (ρ) was estimated to be –0.38, which is a characteristic of a radical reaction.

The reaction of ethers was also studied with $CsSO_4F$ and resulted in cleavage and oxidation to give a mixture of alcohols and aldehydes.[98]

1.9.3 Perchloryl fluoride ($FClO_3$)

Perchloryl fluoride ($FClO_3$) was the first electrophilic fluorination reagent of this type which had larger application in industry. Despite strong electrophilic properties which enable the selective synthesis of organic compounds such as fluoro-steroids,[96] its use in industry is severely limited due to its explosive properties in the contact with organic solvents.

1.10 Xenon difluoride (XeF_2)

Xenon difluoride is a white solid which is very easy to handle and also has a long history of use as a fluorinating agent. Fluorination with this reagent does not always proceed through

an electrophilic pathway. Electrophilic fluorination of various aromatic compounds was only achieved in the presence of an acid to produce monofluorinated compounds regioselectivity.[99] Fluorination of the tertiary site of saturated compounds also proceeds in good yield (adamantane 60%) but with molecules possessing only secondary and primary carbons reactions proceed with low selectivity.

The reaction of xenon difluoride (Figure 1.47) with benzaldehyde proceeds through a Hunsdiecker-like mechanism: decarboxylation followed by fluorination leads to the formation of difluoromethyl-ethers.[100]

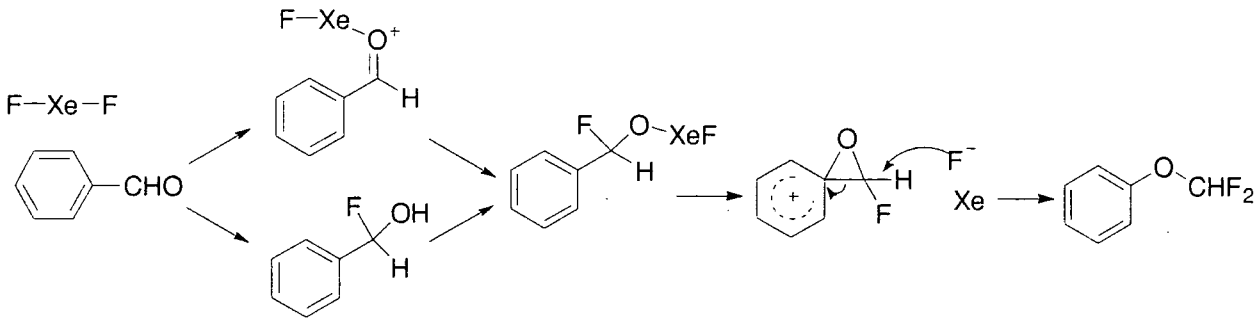


Figure 1.47

1.11 Conclusion

In last few decades, organofluorine chemistry has developed into an important area of organic chemistry due to the versatile applications of fluorinated organic compounds. This class of compounds is rarely found in nature, so many new synthetic methods were developed to enable their synthesis.

Elemental fluorine is a useful reagent for the synthesis of fluorinated and perfluorinated compounds. In comparison to other fluorinating agents, fluorine is the cheapest fluorinating agent (Table 1.6).

Table 1.5 Price of the fluorinating agents

Reagent	F_2	CF_3OF	Selectfluor	Accufluor	XeF_2
Price (£/g)	0.26	35.9	1.49	3.6	41.2

The main limitations for the wider use of elemental fluorine are its toxicity and corrosive properties. Consequently, many electrophilic reagents have been developed as alternatives, and their applications were discussed in this chapter. These reagents are often more selective and simpler to use than elemental fluorine but due to their relatively high price, it is unlikely that they will have any large scale industrial application.

In this thesis, we aimed to establish possible routes for the synthesis of selectively fluorinated hydrocarbon derivatives and aromatic compounds using elemental fluorine. In addition, its relative efficiency is compared to Selectfluor™, commercially available fluorinating agent.

Chapter 2 Fluorination of ethers

2.1 Introduction

Selective direct fluorination of hydrocarbon systems using elemental fluorine has been extensively studied by several groups[34, 45, 46] and is reviewed in this thesis in Sections 1.6.1.5 and 1.7.3. We are interested in exploring the role of functional groups in molecules in the process of fluorination. Fluorination of compounds with electron-withdrawing groups, such as aldehydes, ketones (Figure 2.1. a), esters (Figure 2.1. b), halogens (Figure 2.1 c) and nitriles, have already been studied.[40, 67, 101] Although selectivity was quite poor and the effect of the functional group small, the general observation was that fluorination tends to proceed at the sites further away from electron-withdrawing groups and is, therefore consistent with an electrophilic process.

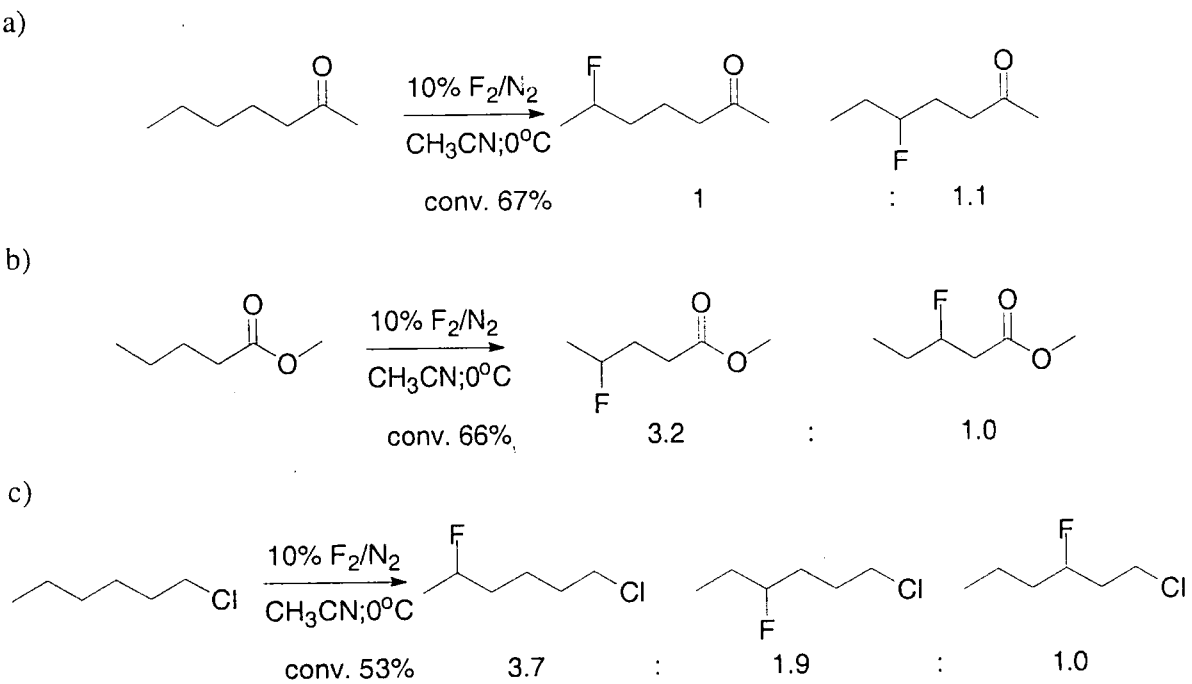


Figure 2.1

This led us to examine reactivity of the derivatives of hydrocarbons bearing electron-releasing groups (Figure 2.2). We chose commercially available ethers and as far as we are aware there is no systematic study of the selective direct fluorination of ethers in the literature.

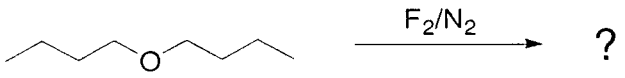


Figure 2.2

This chapter of the thesis presents our novel results concerned with flourination of acyclic and cyclic saturated and aryl-alkyl ethers. The approach that we took primarily involves fluorination with elemental fluorine. Since Selectfluor™ is known to be an electrophilic reagent, we aimed to obtain more information concerning fluorination mechanisms by comparison of the two fluorinating agents. We assessed the efficiency and selectivity of both reagents. The description of the apparatus used to perform direct fluorination reactions is given in Chapter 7.

2.1.1. Synthesis of fluorinated ethers

In this section, a short overview of recently published methods of carbon fluorine bond formation for synthesis of fluorinated ethers is presented.

Perfluorination of ethers and polyethers using elemental fluorine via radical mechanism was reported by Chambers (Figure 2.3).[46]

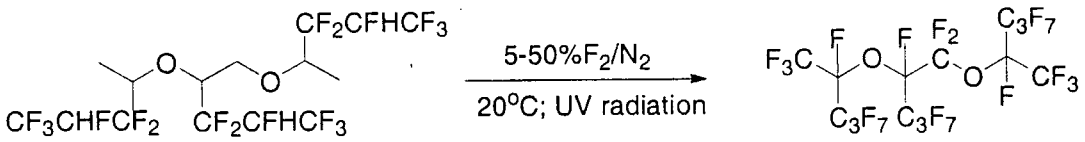


Figure 2.3

The reaction was aided by thermal dissociation of fluorine molecules in a hot nickel tube at 140°C. In addition, radical perfluorination assisted by photo-initiation was achieved and resulted in isomerically pure perfluorinated ethers. Substrates containing a larger number of fluorine atoms have proved to be very stable compounds even when 50% F_2 was used.

Also, the substrates were found to be stable towards the considerable amount of hydrogen fluoride produced in this reaction. This stability is evidently provided by the presence of fluorine atoms in the molecules, since greater losses of substrates with less fluorine atoms were observed using the same reaction conditions.

The synthesis of fluoro-ethers was widely studied because of a huge potential for application as lubricants, inert fluids, inhalation anaesthetics, cleaning solvents and also for replacement of CFCs, HCFCs, and PFCs.[102]

Selective fluorination of polyfluorinated ethers using elemental fluorine was achieved by Sekya[103] and a detailed description of this study is presented in Section 1.6.1.5. Monofluorination of the fluorinated ethers using high-valency metal fluorides (Figure 2.4) was reported by Kurosawa (Figure 2.4).[104]

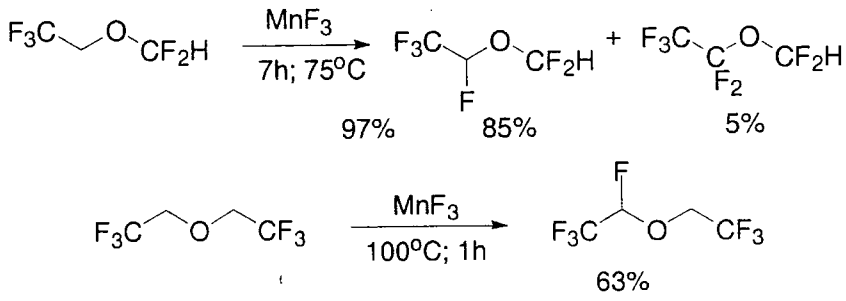


Figure 2.4

Various metal fluorides were assessed and reactivity was determined to be in the following order: MnF_3>CoF_3>$KCoF_4$. However, this method did not show suitable for fluorination of non-fluorinated ethers, resulting in a cleavage of C-O and C-C bonds.

Electrophilic fluorination of aryl-ethers was achieved using the "N-F" class fluorinating agents Selectfluor™, Accufluor™ and N-fluoro-bis(phenylsulphonyl)amine.[75] Although it is possible to achieve good conversion, regionselectivity was very poor. Two products were obtained, with fluorine atoms in *ortho* and *para* to the ether group. When diphenylether was used as a substrate (Figure 2.5) similar conversion was achieved by each reagent (42-73%).

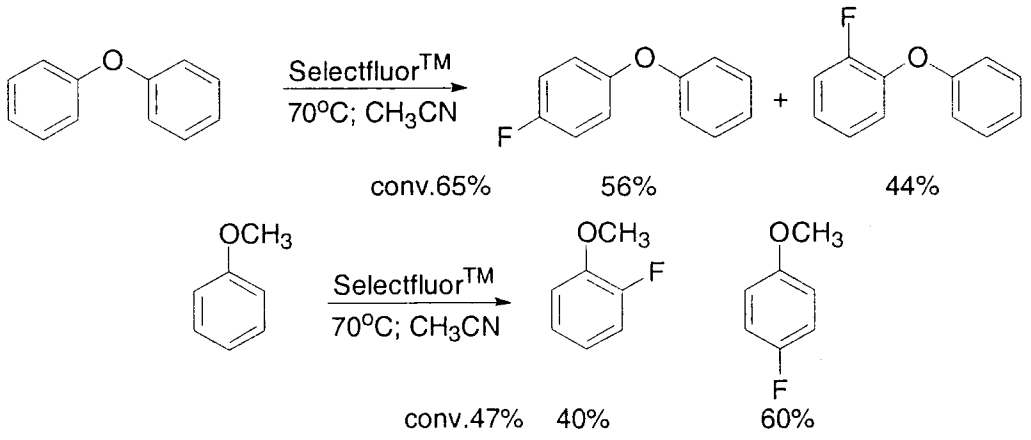


Figure 2.5

Efficient synthesis of monofluorinated saturated cyclic ethers was achieved by electrochemical fluorination (Figure 2.6).[105]

a) b)

Figure 2.6 i: -2e, $Et_4NF{\cdot}4HF$; 150 mA/cm^2

Since the reaction was performed in solvent-free conditions, the products were easily isolated by simple distillation of the electrolytic mixture.

Recently reported nucleophilic methods for synthesis of monofluorinated and polyfluorinated ethers include the use of Deoxyfluor™ reacting with arylgluoxsal hydrates;[106] diisopropylethyl amine mono-hydrogen fluoride, which is based on the Halogen exchange reaction (Halex).[107] In addition fluorinated ethers are often synthesized by addition of fluorinated alcohols or ethers to olefins,[108, 109] but in this thesis only methods involving C-F bond from C-H formation are relevant, so these methods are not discussed further.

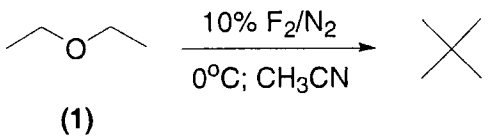
We conclude that selective fluorination of the non-fluorinated saturated ethers is very difficult due to the cleavage of C-C and C-O bonds. The only successful method developed so far is electrochemical fluorination of cyclic ethers.

2.2 Fluorination using elemental fluorine

In this section, overview and discussion of our results dealing with the reaction of elemental fluorine with saturated and aromatic ethers are presented. Proposed mechanism is also described at the end of this section.

2.2.1 *n*-Diethyl ether

Elemental fluorine was passed through a solution of *n*-diethyl ether **(1)** in acetonitrile but was aborted after 10 minutes due to the occurrence of a vigorous reaction (Figure 2.7).



(1)

Figure 2.7

Diethyl ether is a compound with a low boiling point, so it is possible that part of the substrate evaporates despite the presence of external cooling and a vigorous reaction starts proceed in the gas phase.

2.2.2 *n*-Dipropyl ether

The direct fluorination of *n*-dipropyl ether in acetonitrile was performed by using 3 equivalents of fluorine at 0°C (Figure 2.8). The ^{19}F NMR analysis of the crude product showed the presence of many fluorinated products and the conversion was estimated to be 69%. The two main products are α-fluoropropyl ether **(4)** and 2-fluoro-1-(2-fluoro-1-propoxy-propoxy)-dipropyl ether **(3)** in the ratio 1:1.9, respectively.

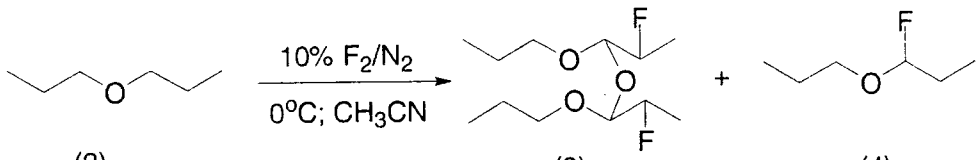


Figure 2.8

Only product **(3)** was isolated by column chromatography as a mixture of diastereoisomers. The ^{1}H NMR spectrum was not found to be particularly informative due to the overlap of resonances. Comprehensive proof of the compound structure was provided by the ^{13}C NMR (Figure 2.9), where the C-β was found to be a doublet having a coupling constant characteristic of $^{1}J_{CF}$ coupling (171.2Hz) and C-α and C-γ as two doublets with coupling constants 26.7 and 21.0 Hz, respectively indicative of $^{2}J_{CF}$ coupling.

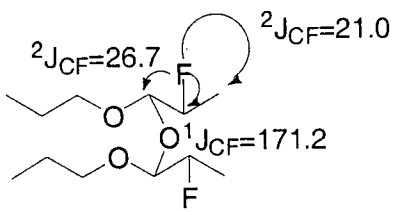


Figure 2.9

Furthermore, monofluorination of one *n*-dipropyl ether unit of this unusual product **(3)** was proven by the presence of three singlets in the ^{13}C NMR spectrum, indicative of a non-fluorinated propyl group. Another proof of the structure was achieved by mass spectrometry, which shows that the molecular mass of the compound is consistent with a structure containing the two monofluorinated units connected by an oxygen bridge. Beside the required molecular ion, the spectrum also shows fragments of 170, 111 and 95 *m/z*, which are in agreement with mass of fragments a), b) and c) (Figure 2.10).

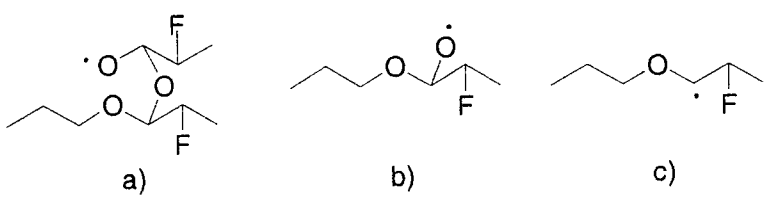


Figure 2.10

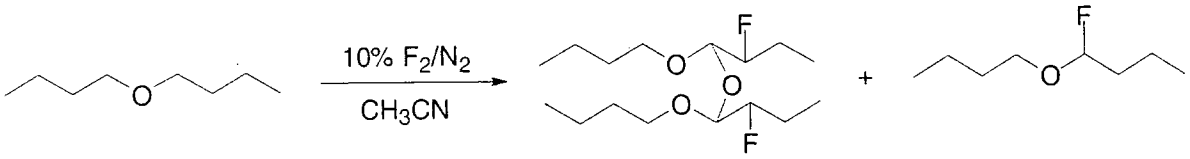
Elemental analysis of the pure product could not be obtained because if was difficult to separate it from the solvent, completely. Its purity was confirmed by GC.

Identification of the α-fluorinated dipropyl ether (**4**) was based on ^{19}F NMR in which fluorine resonances were found to be a doublet of triplets with coupling constants 59.8 Hz and 9.2 Hz, which are characteristic of $^{1}J_{HF}$ and $^{3}J_{HF}$ coupling, respectively.

We conclude that fluorination of dipropyl ether proceeds with good conversion but low selectivity. The main product (**3**) is quite unexpected and the mechanism for its formation is discussed later in this chapter, after all the findings are presented which led to its proposal.

2.2.3 *n*-Dibutyl ether

Fluorination of *n*-dibutyl ether (**5**) was carried out in dry acetonitrile with 2 equivalents of 10% fluorine diluted in nitrogen at 0°C for 19 h (Figure 2.11). The ^{19}F NMR spectrum of the reaction mixture showed a multiplet at chemical shift −127.8 ppm as a main peak. Aqueous work up to neutralize eliminated hydrofluoric acid with base ($NaHCO_3$) resulted in a crude material. The GC analysis of the crude product revealed a several by-products.



(5) (6) (7)

Conv. 57% 31% 17%

Figure 2.11

Two main products were detected in the ^{19}F NMR spectrum. Besides the resonance at −127.1 ppm, a peak at −196.4 ppm (ratio 1:3.7) was observed. Purification of the crude material by column chromatography yielded a mixture of diastereoisomers of 2-fluoro-1-(2-fluoro-1-butoxy-butoxy)-dibutyl ether (**6**).

In the ^{13}C NMR spectrum, 8 carbon resonances which correlate to the symmetric structure of the product (**6**) are found. The spectrum is very similar to the spectrum of

product (**3**). In addition a doublet with coupling constant of 4.4 Hz ($^3J_{CF}$) was found which correlates to the terminal carbon. The second product, 1-fluorodibutyl ether (**7**) (Figure 2.11), could not be isolated by column chromatography and the confirmation for the formation of this product was made according to mass spectrometry and ^{19}F NMR data of the crude product. The similar reaction was carried out with 3 equivalents of fluorine and without neutralization with $NaHCO_3$ during the work-up procedure. The results are shown in Table 2.1.

Table 2.1 Fluorination of *n*-dibutyl ether using elemental fluorine

Entry	Fluorine : Substrate ratio	Base (work-up)	Conversion (%)	Yield (6) (%)	Yield (7) (%)[a]
1	2	$NaHCO_3$	57	32	17
2	3	$NaHCO_3$	79	38	28
3	3	–	76	49	10

a) calculated yield, estimated according to ^{19}F NMR spectrum of the crude product.

The reaction using 3 equivalents of fluorine (Table 2.1, entry 2.) resulted in an improvement in conversion and the ratio between (**6**) and (**7**) was found to be 1.4:1. A higher conversion affords easier elimination of hydrofluoric acid, which we assume is involved in the mechanistic pathway of synthesis of product (**6**).

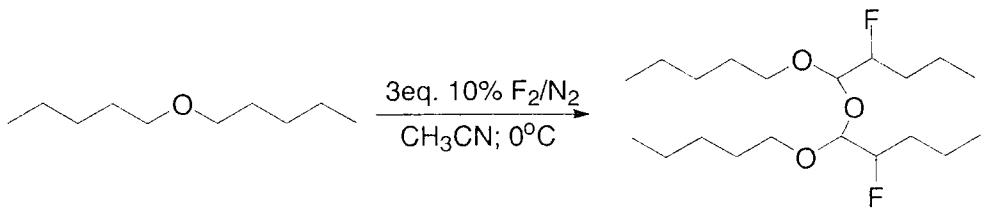
The next experiment (Table 2.1, entry 3) was also carried out with 3 equivalents of fluorine, but base ($NaHCO_3$) was not used during work-up procedure. The acidic environment yielded 2-fluoro-1-(2-fluoro-1-butoxy-butoxy)-dibutyl ether (**6**), as the main product (49%).

We can conclude that the reaction proceeds in an analogous fashion to the reaction of *n*-dipropyl-ether with elemental fluorine and only the stable product (**6**) was isolated. Conversion can be enhanced by increasing the relative amount of fluorine.

2.2.4 *n*-Dipentyl ether

Fluorination of *n*-dipentyl ether (**8**) was performed with the previously optimized conditions using 3 equivalents of elemental fluorine (Figure 2.12). The organic compounds

were extracted without previous neutralization of the aqueous phase with base. The ^{19}F NMR spectrum of the crude product showed the presence of several fluorinated products of which the major product was found to be 2-fluoro-1-(2-fluoro-1-pentyloxy-pentyloxy)-dipentyl ether **(9)** in 56% conversion.



(8) 43% yield 56% conv. **(9)**

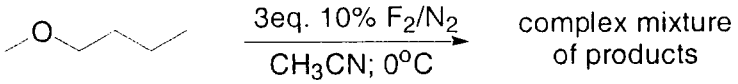
Figure 2.12

As in the previously described systems, mixture of diastereoismers was also formed in this reaction. In the ^{13}C NMR spectrum, there are 10 signals correlating to the 10 carbon atoms. Splitting of the signals due to the presence of fluorine is very similar to the previously described molecules **(3)** and **(7)**. However, there is a doublet a with a coupling constant of 2.1 Hz, which is characteristic of four bonds coupling and a chemical shift of 14.0 ppm, characteristic of CH_3 sites.

We can conclude that fluorination of the *n*-dipentyl ether proceeds with moderate conversion. Although this molecule possesses more reactive sites than compounds **(2)** and **(5)**, fluorination mainly occurs at the β-position and selectivity is retained as in previous cases.

2.2.5 Methyl-butyl ether

Fluorination of the unsymmetric molecule such as methyl-butyl ether **(10)** was carried out by using 3 equivalents of fluorine (Figure 2.13). The ^{19}F NMR spectrum of the crude product showed the presence of a large number of products which could not be identified or purified by column chromatography.

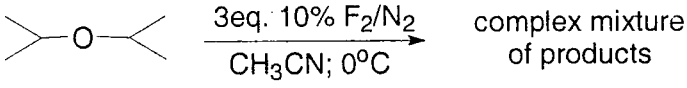


(10)

Figure 2.13

2.2.6 Isopropyl ether

The reaction was carried out using 3 equivalents of fluorine which was passed through solution of isopropyl-ether (**11**) in dry acetonitrile (Figure 2.14). According to GC, there were more than 10 products with the yield of less than 8% for each (which could not be identified). Also noticeable amount of tar was formed during this reaction.



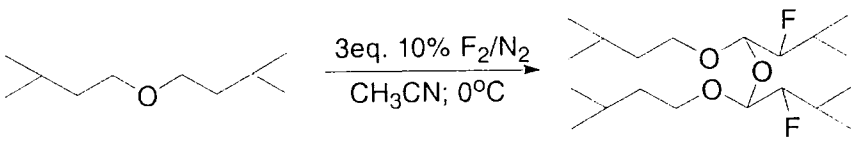
(11)

Figure 2.14

This indicates that the electrophilic fluorination of ethers with fewer carbon atoms proceeds with poor selectivity or led to formation of unstable products.

2.2.7 Isoamyl ether

Fluorination of isoamyl ether (**12**) using 3 equivalents of elemental fluorine resulted with 46% conversion (Figure 2.15). The ^{19}F NMR spectrum of crude product shows presence of one main product, 2-fluoro-1-[2-fluoro-3-methyl-1-(3-methyl-butoxy)-butoxy]-isoamyl-ethers (**13**) and several minor products in 41% yield.



(12) (13)

conv. 46% 41%

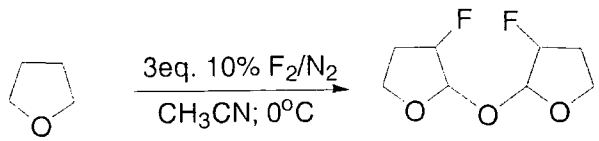
Figure 2.15

Pure product **(13)** was isolated by distillation using Kugel-Rohr apparatus and its identification was achieved by ^{1}H NMR, where the signal of the hydrogen attached to the fluorinated β-carbon was found to be a triplet of doublets with coupling constants 47.2 Hz, 6.2 Hz and 3.6 Hz due to coupling with fluorine and neighboring hydrogens. The most shifted resonance (δ=4.4 ppm) was assigned to C-α next to the oxygen bridge. Furthermore, the ratio of the peak areas in the ^{1}H NMR spectrum is in agreement with the proposed structure. Further confirmation of the structure was obtained by ^{13}C NMR spectrum which is very similar to the spectrum of product **(6)**.

To summarise, fluorination of isoamyl ether proceeds with higher selectivity than fluorination of isopropyl ether although isoamyl ether possesses additional reactive sites such as a tertiary carbons. This implies that result of the reaction depends mainly on the stability of the products.

2.2.8 Tetrahydrofuran

Fluorine gas was passed through a solution of tetrahydrofuran in acetonitrile (Figure 2.16). In the ^{19}F NMR spectrum of the crude product, a peak with chemical shift −184.5 ppm was found and correlates to the new compound. Analogous to the reaction with acyclic ether, substitution of hydrogen with fluorine occurred at β-position to the oxygen.



(14) (15)

69% conv. 34%

Figure 2.16

After purification by column chromatography, the product 3-fluoro-2-(3-fluoro-tetrahydrofuran-2-uloxy)-tetrahydrofuran **(15)** (Figure 2.16) was isolated as a mixture of diastereoisomers. In the ^{13}C NMR, there are 4 signals, which correlate to the symmetric structure of the product. Coupling constants of the isolated product **(15)** are also very similar to the coupling constants of the product **(6)**.

To summarise we found that cyclic ethers react with elemental fluorine in a similar manner to acyclic ethers but with lower selectivity.

2.2.9 Aldal acetals

Non-fluorinated analogues having the bonding array $RC(OR_1)HOC(OR_1)HR$ or an α,α'-dialkoxy ether have already been synthesised. The name of this class of compounds, aldal acetals was proposed by Hurd.[110] They are usually synthesised in two step reactions (Figure 2.17) starting from formaldehydes, which are converted into α,α'-dichlorodialkyl ethers followed by subsequent reaction with sodium alkoxides.[111]

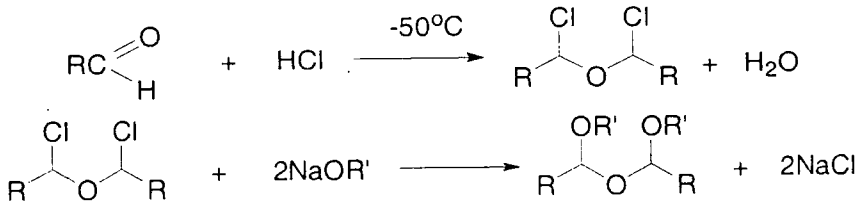


Figure 2.17

Reported overall yields for a range of the *n*-alkyl and cyclic aldal acetals were between 12% and 37%. This class of compound is known for its low stability in the presence of

water and in acidic media. Their hydrolysis was studied by Oon[112] and a proposed mechanism is shown below in a Figure 2.18.

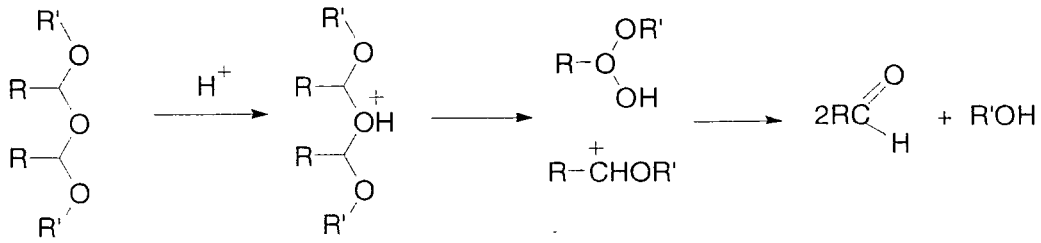


Figure 2.18

The hydrolysis is initiated by the protonation of oxygen and finally results in production of aldehydes. The half life of most of these aldal acetals were estimated to be from several minutes to several hours at room temperature depending on the pH value.[111] Thanks to this property, aldal acetals can be used as precursors for acetaldehydes which found application in food industry as fragrances and flavours. A particular advantage is the controlled release rate of the acetaldehydes, allowing the product to keep for a longer period the desired fresh flavour, aroma or fragrance.

Our fluorinated analogues are found to be quite stable, resistant to hydrofluoric acid, eliminated during fluorination and water, from the exposure during aqueous work-up procedure. The speculated reason for the increased stability is due to the presence of fluorine which strongly withdraws electrons from neighboring oxygens (Figure 2.19) which are therefore less susceptible towards protonation.

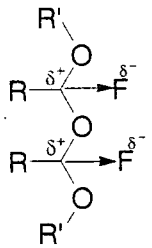


Figure 2.19

The increased stability of the polyfluorinated ethers has already been reported[44] even though large amount of HF was produced in process of perfluorinaition (Section 4.2).

Aldal acetals possess usually several chiral centers. In this reaction, a mixture of diasteroisomers was isolated.

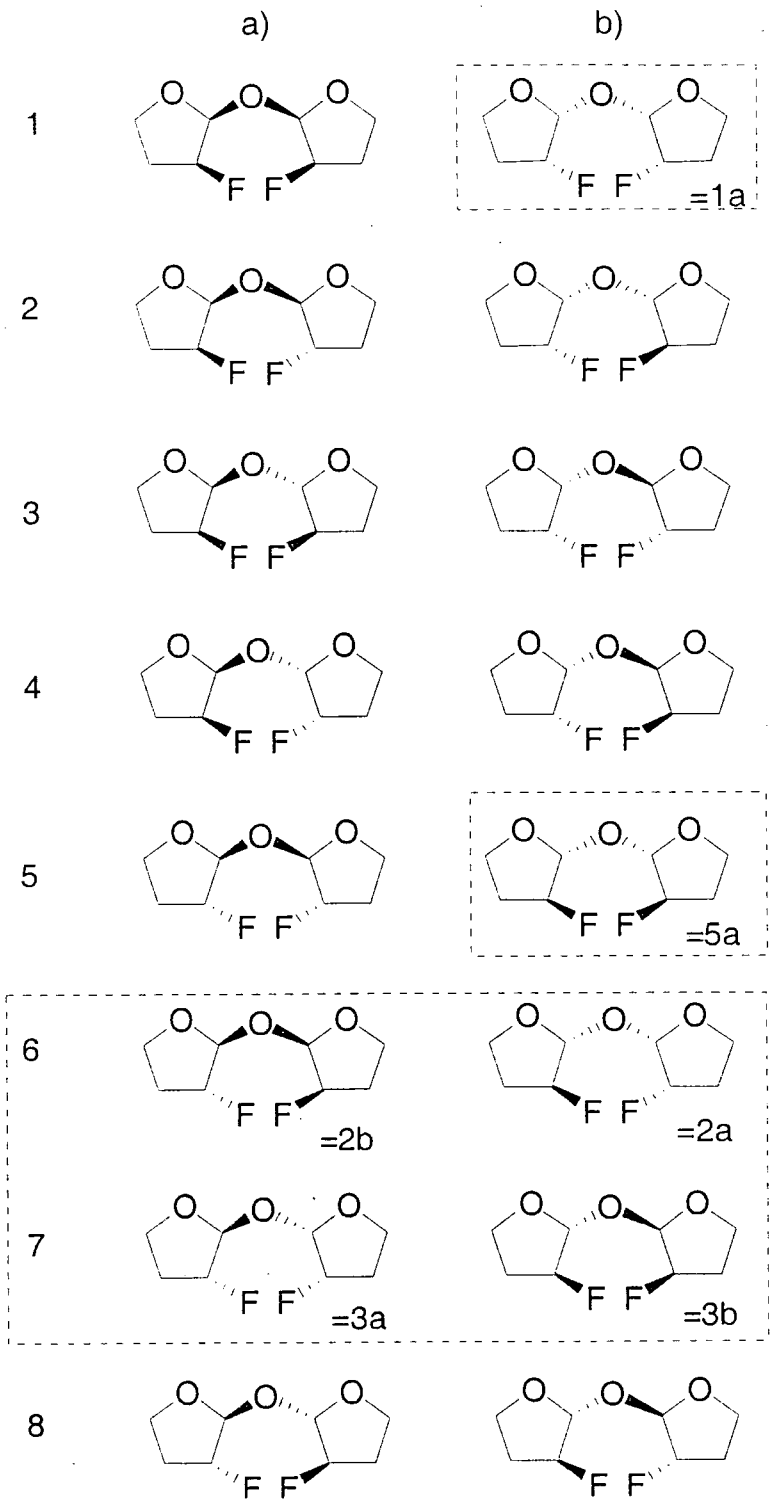


Figure 2.20

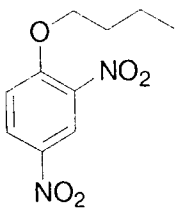
The maximum number of stereoisomers for a molecule that contains four chiral centres is 16 (2^n). However, in this case there are some repetitions: 6 and 7 (Figure 2.20) are equal to the 2 and 3, respectively. Also, the molecule contains a plane of symmetry, so we can conclude that theoretically, this compound could have 2 meso-stereoisomers (1 and 5) and 4 pairs of enatiomers (2, 3, 4 and 8). Although theoretically it is possible to detect 6 diastereomers in GC, we usually found three or four main diastereomers as the most abundant.

2.2.10 Summary

The reaction of elemental fluorine with alkyl ethers proceeded in good conversion and moderate selectivity. In all examples, the main product was found to be an aldal acetal. The reaction of alkyl ethers with elemental fluorine proceeds through a complex mechanism and we needed more information to determine a final mechanistic pathway. The β-position in alkyl ethers is not the most electron-rich position. Despite that the main product is always fluorinated at the β-position. The main question is what is the driving force that governs the formation of aldal acetals as the only stable product. To provide more information we decided to use aryl-alkyl ethers for fluorination studies.

2.2.11 Aryl-alkyl ethers

Fluorination of arylalkyl ethers has been widely studied.[75] It is known that the benzene ring is a good nucleophile and that the presence of any of electron-donating substituents like alkoxy groups will direct fluorination onto the ring. The presence of a deactivating group makes the benzene ring more resistant towards fluorination. The ether we chose consists of a deactivated benzene ring with two nitro groups and a butyl group **(16)** (Figure 2.21).



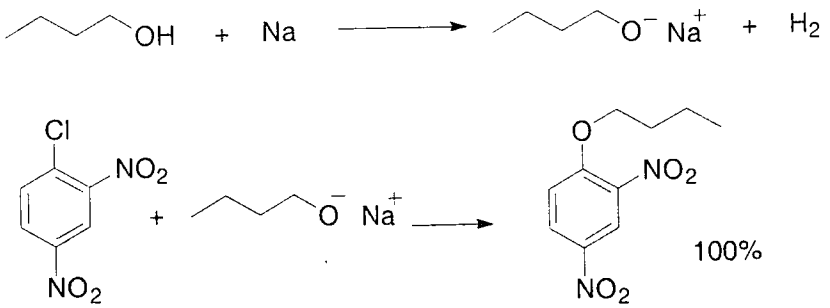
(16)

Figure 2.21

We expected that bulky aryl groups would prevent formation of the aldal acetals. Also, we presume that the most reactive site is in alkyl part of the molecule, where initial fluorination may occur. In addition, we aimed to compare the reactivity of aryl-alkyl ethers with dialkyl ethers in the reactions with fluorine.

2.2.11.1 Synthesis of 1-butoxy-2,4-dinitro-benzene

Synthesis of 1-butoxy-2,4-dinitro-benzene was carried out by the Williamson synthesis (Figure 2.22). In the first step, sodium was added to 1-butanol to form sodium butoxide. 1-Chloro-2,4-dinitro-benzene was added to the reaction mixture and maintained under reflux until complete conversion. The reaction was followed by TLC and showed only one product.



(16)

Figure 2.22

The product was purified by simple recrystallisation and characterized. This product was used as a starting material in experiments with both elemental fluorine and Selectfluor™.

2.2.11.2 Fluorination of 1-butoxy-2,4-dinitro-benzene

The reaction was carried out by passing 3 equivalents of fluorine through a solution of 1-butoxy-2,4-dinitro-benzene (**16**) and resulted in 81% conversion (Figure 2.23). The ^{19}F NMR spectra showed only one resonance (doublet) with a chemical shift of −121.0 ppm with coupling constant of 9.97 Hz. This implies that fluorination occurred selectively at the ring.

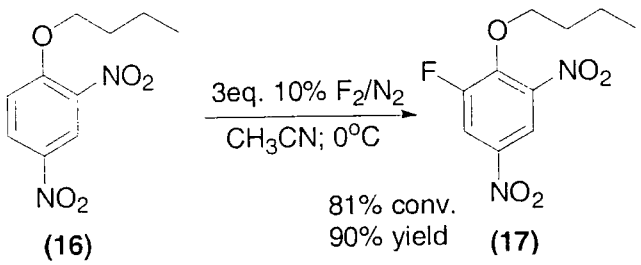
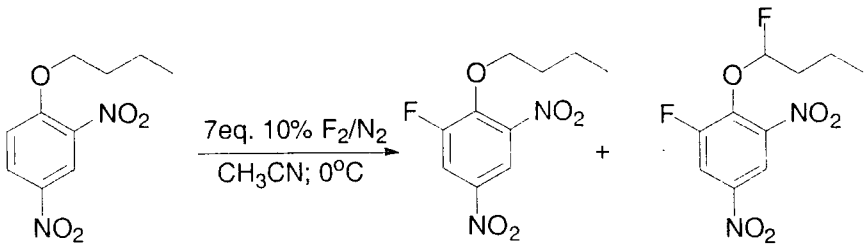


Figure 2.23

The product was isolated and subsequently identified as 6-fluoro-1-butoxy-2,4-dinitrobezene (**17**). Important proof of this structure was obtained by ^{1}H NMR and showed the absence of a peak at 7.2 ppm (doublet), which occurred in the starting material spectrum and correlates to the proton bonded in the *ortho*-position to the butoxy group. Further evidence was derived from carbon-fluorine coupling constants. The C-6 was found to be a doublet with a coupling constant of 154.8 Hz. Furthermore, alkyl α-carbon was found to be doublet with coupling constant 8.1 Hz, which is slightly higher than expected probably due steric proximity to the fluorine.

The reactivity of the aromatic ring (even with the deactivating nitro-groups) towards electrophilic fluorination appeared to be higher than at the saturated site of the ether.

By increasing the amount of fluorine (7 equivalents) used in the reaction, aromatic substitution proceeded until the substrate was consumed completely (Figure 2.24).



(16) **(17)** **(18)**

Figure 2.24

Monofluorinated product **(17)** obtained in the reaction was accompanied with formation of a difluorinated product, which, after purification, was determined to be α-fluorobutoxy-1-fluoro-2,4-dinitro-benzene **(18)**.

The ^{1}H NMR spectrum of **(18)** shows only two aromatic protons and the presence of the only one aliphatic proton at α-carbon. In the ^{19}F NMR spectrum, we found two fluorine peaks at chemical shifts −121.2 ppm and −124.3 ppm in ratio 1:1. The more shifted peak (−124.3 ppm) was found to be doublet of doublet of triplets with coupling constants of 60.5 Hz, 18.1 Hz and 12.1 Hz that agrees with two bond ($^{2}J_{HF}$) couplings to the geminal proton, fluorine-fluorine coupling and a three bond coupling to the two protons from the adjacent carbon, respectively. In the ^{13}C NMR spectrum, C-α was found to be a doublet with a $^{1}J_{CF}$ coupling of 251.1 Hz, while resonances of carbons from the aromatic part of the molecule are similar to those found in the spectrum from monofluorinated product **(17)**.

We found that reactivity of the aromatic part of the molecule is more pronounced than the aliphatic part, despite the two strongly deactivating nitro-groups attached to the ring. When fluorination on the benzene ring was completed and an additional amount of elemental fluorine was introduced into the reaction mixture, we found that the reaction occurs at the α-position to the oxygen. This finding is very important since this indicates that the most reactive position in the aliphatic ether chain is at carbon adjacent to oxygen and supports the mechanism described in the next section.

2.2.12 Discussion of the reaction mechanism

Fluorination using elemental fluorine may proceed via a radical, single electron transfer mechanism (SET), or an aliphatic electrophilic substitution and a detailed overview is presented in Section 1.6.1.3.

We have postulated the following mechanism for the formation of the aldal acetals (Figure 2.25), where initial fluorination occurred at the α-position to the oxygen.

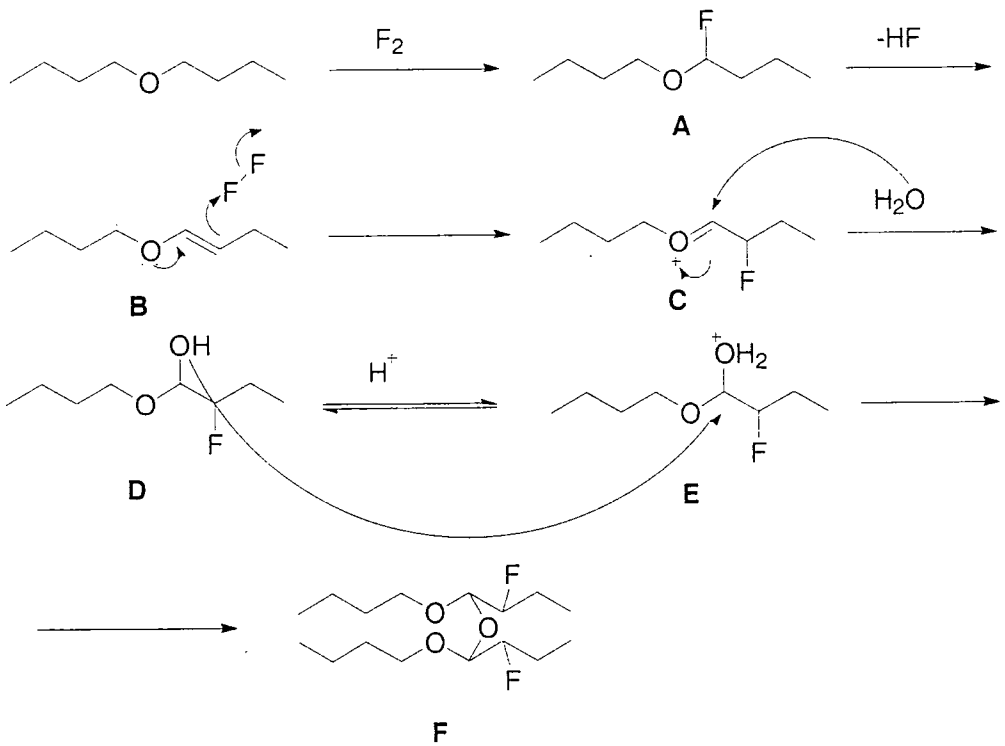


Figure 2.25

Consequently, we assume that the reaction proceeds via an electrophilic mechanism and results in the formation of a pentacoordinate transition state (Figure 1.5), which is stabilized by electron donation from the lone pairs on the oxygen (Figure 2.26).

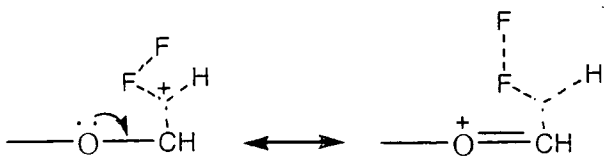


Figure 2.26

The moderate selectivity often suggests that reaction may proceed via a radical process. We have to consider however that some by-products may be produced by cleavage of the ether in the acidic environment or as intermediates formed in the postulated mechanism.

After elimination of HF, unsaturated ether (**B**) is formed. In the next step, further fluorination occurs to give the oxonium ion (**C**). During the work up procedure, the oxonium ion interacts with water and forms a hydroxyl group at the α-position to the oxygen. In an acidic environment, the hydroxyl group is protonated and both forms exist in solution. These two intermediates react to form the polyacetals. Alternatively, the oxonium ion (**C**) interacts with intermediate (**D**) to give the final product (**F**).

The ^{19}F NMR spectra show that the distribution of the products (**A**) and (**F**) changes during work up procedure in a favour of aldal acetals (**F**). The presence of the final product (**F**) in the reaction mixture, before the aqueous work-up procedure, is probably caused by moisture in the acetonitrile which is notoriously difficult to dry. Also, this fact suggests that part of the process occurs in the presence of water.

Further confirmation that initial fluorination proceeds next to oxygen is gained from reaction the of 1-butoxy-2,4-dinitro-benzene (**16**) with elemental fluorine. After additional deactivation of the ring with fluorine, reaction proceeds at the α-position to the oxygen.

Alternative mechanistic pathway of the initial fluorination is the Pummerer rearrangement, which is presented in Section 1.7.3 in the reaction of thio-ether derivative with Selectfluor™. The reaction of elemental fluorine with alkyl ethers may also proceed via a similar pathway (Figure 2.27)

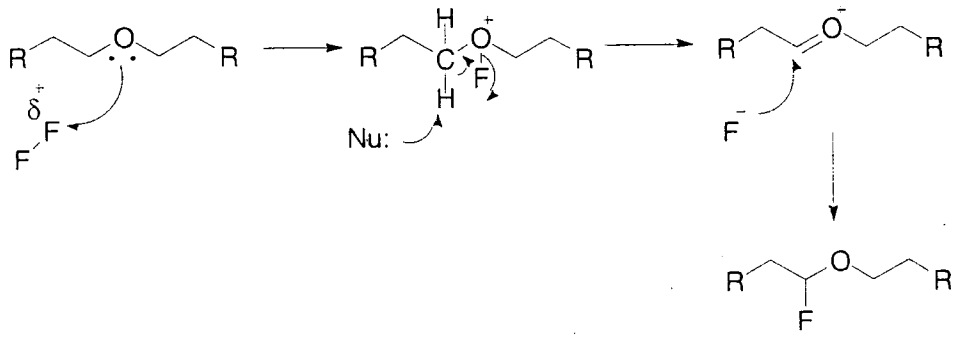
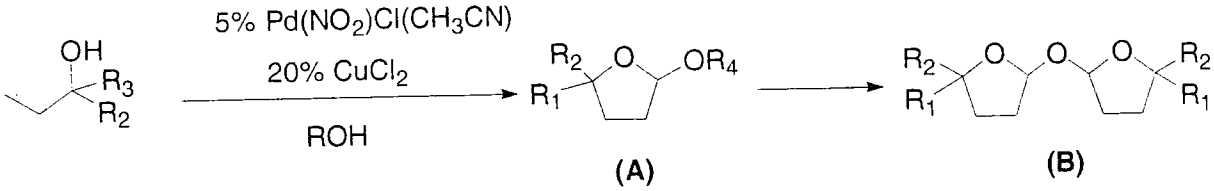


Figure 2.27

Initial fluorination occurs at the oxygen followed by elimination of the HF and formation of an oxonium ion. The problem with this proposed mechanism is that the repulsion between fluorine and oxygen lone pair electrons is much higher than between sulphur and fluorine due to the smaller size of the oxygen atom, making this mechanistic pathway less probable.

Formation of acetal aldals (Figure 2.28) was reported by Feringa[113] in the catalytic oxidation of homoallylic alcohols. The oxidation reaction was performed using a Palladium-nitro catalyst in the presence of Copper(II) chloride in alcoholic solvents giving an α-alkoxy-THF (**A**).



(A) **(B)**

Figure 2.28

The author has commented that another product, bis dihydrofuran **(B),** was formed during isolation of product, but a suggestion of the mechanistic pathway was not provided.

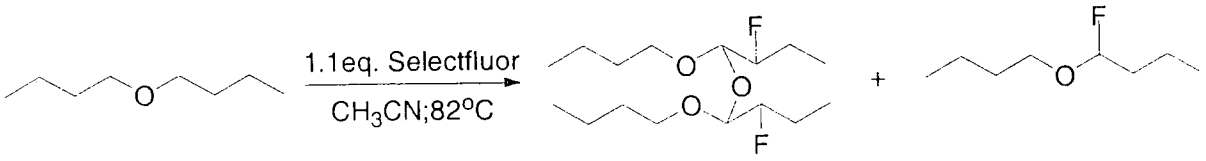
2.3 Fluorination with Selectfluor

In this section, the results of the fluorination of ethers using Selectfluor™, a commercially available member of the "N-F" class of electrophilic reagents are presented. We expected to acquire supportive evidence of our hypothesis of the mechanism.

2.3.1 *n*-Dibutyl ether

Fluorination of *n*-dibutyl ether using Selectfluor™ was carried out in dry acetonitrile at reflux temperature for 18 h (Figure 2.29). ^{19}F NMR analysis of the reaction mixture showed peaks at chemical shifts of −124.8 ppm and −194.3 ppm in 2:1 ratio, similar to the

reaction with elemental fluorine. In the ^{19}F NMR spectrum of the crude product, there were several resonances at −118.1 ppm, −193.2 ppm and −196.4 ppm (ratio 1.3:3.1:23.4).



(6) **(7)**

Figure 2.29

Table 2.2 Fluorination of *n*-dibutyl ether using Selectfluor™

Entry	Selectfluor : Substrate ratio	Base (work-up)	Conversion (%)	Yield (**6**) (%)	Yield (**7**) (%)
1	1.1	$NaHCO_3$	67	17	72
2	1.1	-	72	11	81

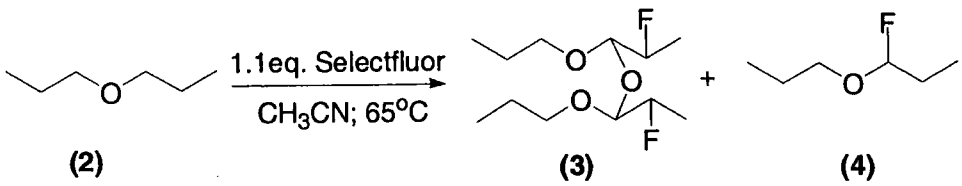
In comparison with the fluorination with elemental fluorine, the reaction with Selectfluor™ resulted in the same products, with a slightly higher conversion (67%), but moreover, with an improved selectivity (Table 2.2). Purification of the crude material by column chromatography yielded a pure product, 2-fluoro-1-(2-fluoro-1-butoxy-butoxy)-dibutyl ether **(6)** (Figure 2.29).

In the experiment which does not employ neutralization during the work-up procedure the yield was slightly improved (Table 2.2, entry 2). We performed the reaction with acetonitrile that contains small amounts of water and the reaction proceeded with a low conversion but a similar selectivity. Interestingly, ^{19}F NMR spectrum of the reaction mixture (before aqueous work-up) procedure shows the presence of the main product, 2-fluoro-1-(2-fluoro-1-butoxy-butoxy)-dibutyl ether **(6)** and just traces of the other products (ratio 6.1:1) implying involvement of water in its formation.

We can conclude that the reaction of Selectfluor™ proceeds with *n*-butyl ether in high conversion and yield to give one main product 2-fluoro-1-(2-fluoro-1-butoxy-butoxy)-dibutyl ether **(6)**. Based on these results, we can reason that the reaction of ether with Selectfluor™ and elemental fluorine proceeds by a very similar mechanistic route and that the formation of product is assisted by the presence of water.

2.3.2 *n*-Dipropyl ether

Fluorination of *n*-dipropyl ether (**2**) by Selectfluor™ was carried out in dry acetonitrile at 65°C for 18 h (Figure 2.30). Fluorination resulted in a relatively high conversion of 72% and purification yielded only one product. In the ^{19}F NMR spectrum, there was one main peak at –186.3 ppm which correlates to the –CHF– moiety.



(2) (3) (4)

Conv. 74% 63% 9%

Figure 2.30

Purification of the crude product by Kugelrohr distillation yielded 2-fluoro-1-(2-fluoro-1-propoxy-propoxy)-dipropyl ether (**3**) and residual starting material.

The following experiment was carried out with *n*-dipentyl ether to examine and compare selectivity and reactivity by changing the number of $-CH_2-$ groups in the substrate.

2.3.3 *n*-Dipentyl ether

Fluorination of *n*-dipentyl ether (**7**) using Selectfluor™ was carried out in dry acetonitrile at reflux temperature for 18 h (Figure 2.31). The ^{19}F NMR spectrum of the reaction mixture shows a peak at chemical shift –127.8 ppm, as in the reaction with elemental fluorine. After aqueous work-up, the crude material was analyzed by ^{19}F NMR and GC. Two main products were observed by GC. In the ^{19}F NMR spectrum, besides a peak at –126.1 ppm, there were signals –193.2 ppm and –196.4 ppm (1.3:3.1:23.4 ratio). These peaks correlate to new compounds formed during the work-up procedure.

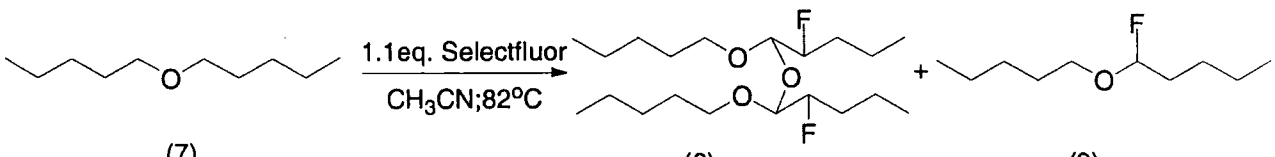


Figure 2.31

The isolated product was 2-fluoro-1-(2-fluoro-1-pentyloxy-pentyloxy)-dipentyl ether **(8).** The structure of this compound was confirmed by NMR analysis and by comparison to the main product of fluorination of *n*-dipentyl ether by elemental fluorine.

We can conclude that fluorination of straight chain symmetrical ethers with Selectfluor™ afford aldal acetals. The aim of the next experiment is to examine the reactivity of cyclic ethers and branched ethers towards Selectfluor™.

2.3.4 Isoamyl ether

Fluorination of isoamyl-ether using Selectfluor™ resulted in a conversion of 62% (Figure 2.32). In the ^{19}F NMR spectrum of the crude product, the main resonance occurs at –205.6 ppm and the yield was estimated to be 56%.

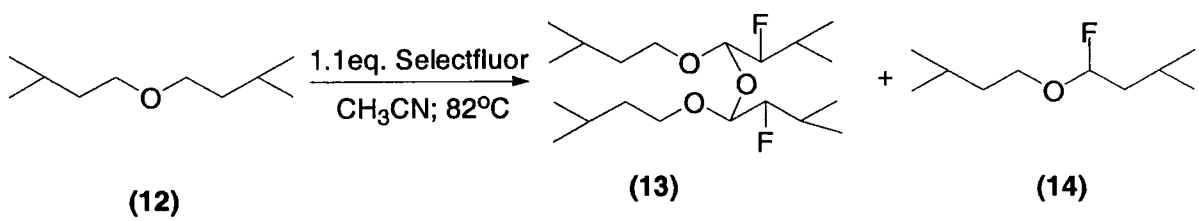


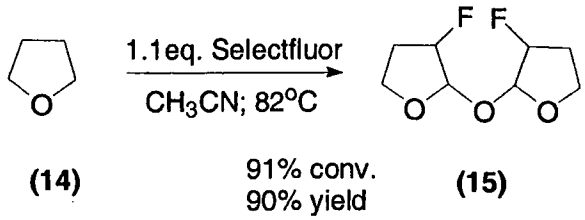
Figure 2.32

The isolated main product was 2-fluoro-1-[2-fluoro-3-methyl-1-(3-methyl-butoxy)-butoxy]-isoamyl ether **(13)**, the same product that was obtained in the reaction with elemental fluorine. Product **(14)** was not isolated but ^{19}F NMR and GC/MS data led us to the proposed structure.

We can conclude that fluorination of isoamyl ether proceed in moderate conversion. The selectivity of the reaction is higher, when the Selectfluor™ was used as fluorinating agent in comparison to elemental fluorine.

2.3.5 Tetrahydrofuran

Fluorination of THF **(14)** using Selectfluor™ was carried out in dry acetonitrile for 18 h (Figure 2.33). In the ^{19}F NMR spectrum, there was one broad main peak at −185.9 ppm which correlates to the -CHF- moiety that is located in the β-position to oxygen.

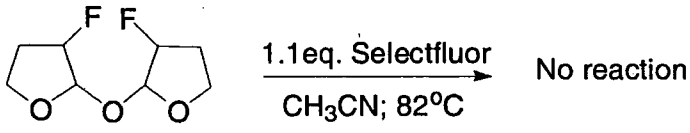


(14) 91% conv. 90% yield **(15)**

Figure 2.33

Purification of the crude product by Kugelrohr distillation gave 3-fluoro-2-(3-fluoro-tetrahydrofuran-2-uloxy) tetrahydrofuran **(15)**.

Since synthesis of the aldal acetal from THF was very efficient, we attempted a reaction of this product with Selectfluor™ to examine whether any further reaction could proceed. Product **(15)** was refluxed with 1.1 equivalents of Selectfluor™ for 18 h (Figure 2.34). According to the ^{19}F NMR spectra and GC/MS no new product was found and the starting material **(15)** was fully recovered.



(15)

Figure 2.34

Only a small amount of black insoluble material was isolated which was possibly a consequence of degradation or polymerisation.

We can conclude that fluorination of tetrahydrofuran with Selectfluor™ provides the same product as in the reaction with elemental fluorine. Conversion is quite high and it is interesting to notice that there is such a big difference in reactivity and selectivity between the cyclic and acyclic straight chain ethers.

2.3.6 1-Butoxy-2,4-dinitro-benzene

Fluorination of 1-butoxy-2,4-dinitro-benzene **(16)** using Selectfluor™ was carried out in dry acetonitrile at reflux temperature for 16 h. According to the ^{19}F NMR spectrum, no fluorinated product was observed.

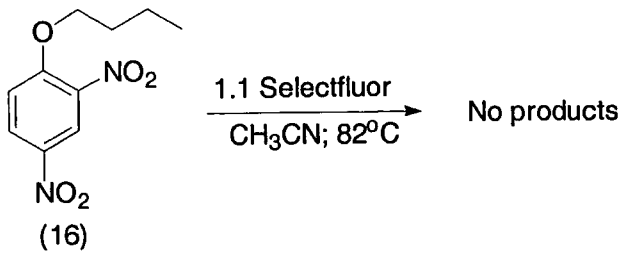


Figure 2.35

The reaction using Selectfluor™ did not occur and the starting material was fully recovered. Selectfluor™ is much less reactive than elemental fluorine in reactions with deactivated aromatic substrates. The incapability of Selectfluor™ to fluorinate deactivated benzene derivatives has already been reported.[66]

2.3.7 Discussion of the reaction mechanism

Since the same products are formed in reactions of ethers with both elemental fluorine and Selectfluor™ similar mechanisms were proposed (Figure 2.36).

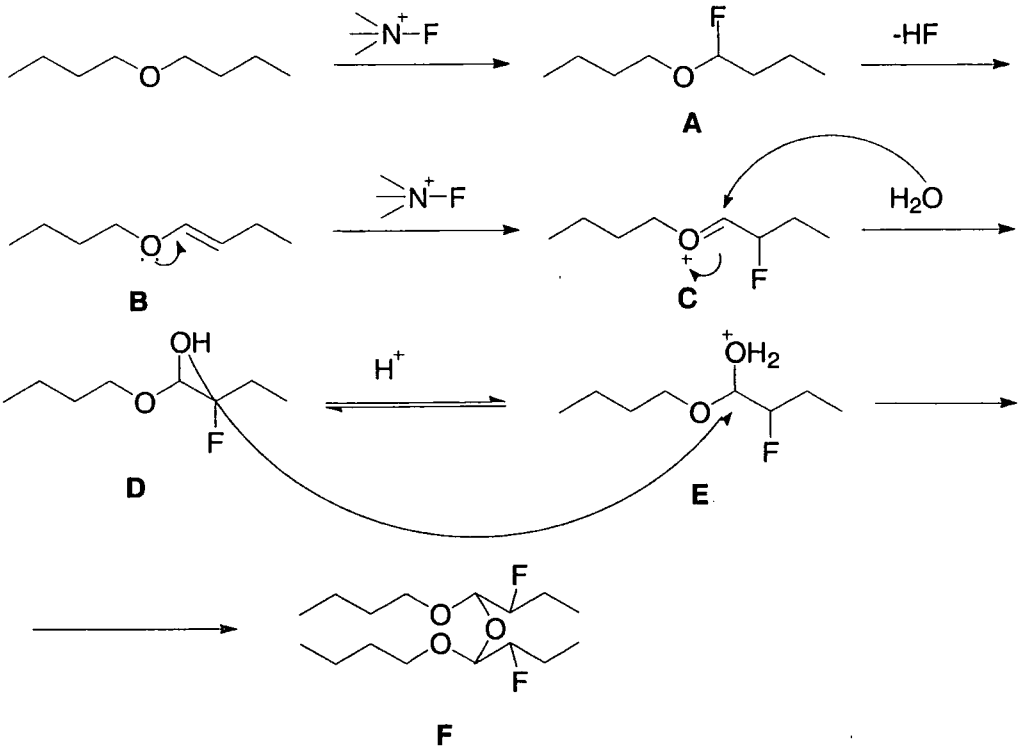


Figure 2.36

Firstly, fluorination occurred at the α-position to oxygen, which is followed by elimination of HF to form unsaturated ether **(B)**. The next step is again fluorination which leads to the formation of oxonium ion **(C)**. During the work up procedure the oxonium ion interacts with water and forms a hydroxyl group at the α-position to oxygen. An acidic environment induces protonation of the hydroxyl group. These two intermediates **(D** and **E)** react and form 2-fluoro-1-(2-fluoro-1-butoxy-butoxy)-1-butyl ether as a product. In this reaction, a mixture of diasteroisomers was also formed. Alternatively, the oxonium ion **(C)** interacts with intermediate **(D)** to give the final product **(F)** (Figure 2.37).

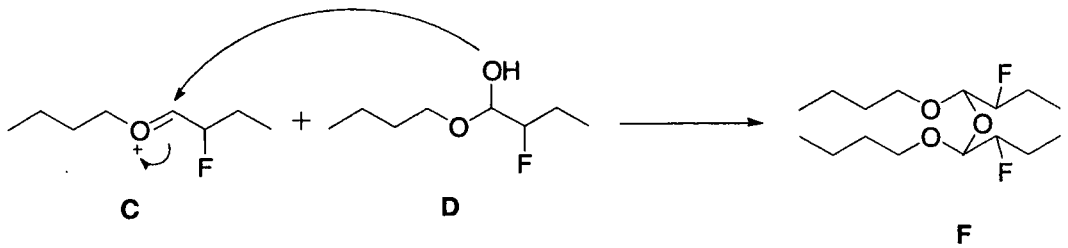


Figure 2.37

As found in the reaction with elemental fluorine, the use of base to neutralize acid produced in the reaction affects the products of the reaction. Furthermore, presence of a small amount of water in the reaction assists formation of the aldal acetals and suggests that molecules of water are directly involved in mechanistic pathway.

The formation of the β-fluorinated oxonium ion intermediate in fluorination using Selectfluor™ has already been reported[82] (Section 1.7.3) and its reactivity towards nucleophiles highlighted.

2.4 Conclusion

We conclude that fluorination of acyclic and cyclic saturated ethers using both elemental fluorine and Selectfluor™ is an efficient method for the synthesis of fluorinated aldal acetals. Since both reagents are providing same products, we assume that initial fluorination with elemental fluorine and also, with Selectfluor™ proceeds via an electrophilic aliphatic process at the carbon next to the oxygen. Using both fluorinating reagents four chiral centers are formed but without any stereoselectivity. The higher selectivity of Selectfluor™ was achieved because elemental fluorine tends to react also with other C-H bonds, via a single electron transfer process.

When an aromatic substrate was used, the reactivity of elemental fluorine was much higher than the reactivity of Selectfluor™. Furthermore, reactivity of the aromatic part of the ether is more pronounced than the aliphatic one, even when strong electron-withdrawing groups are attached to the benzene ring.

Since fluorination of the 1-butoxy-2,4-dinitro-benzene proceeds with high efficiency, we aimed to expand this methodology using other tri-substituted and di-substituted benzene derivatives which have electron-withdrawing groups on the aromatic ring. These novel results are presented in the next chapter.

Chapter 3 Fluorination of deactivated benzene derivatives

3.1 Introduction

Based on the study described in the previous chapter, we concluded that elemental fluorine is a very efficient reagent for fluorination of butoxy-2,4-dinitro-benzene. We decided to expand the methodology to other multi-substituted deactivated benzene derivatives. Various nitro-benzenes and cyano-benzenes were fluorinated and the results are presented in this chapter. A study of benzaldehyde derivatives was more extensive and evolved into a separate chapter.

3.1.1 Synthesis of fluoroaromatic compounds

In this section the most notable ways of synthesising fluorinated benzene derivatives are presented with particular attention to those with deactivated substituents.

Electrophilic fluorination of aromatic compounds has been widely studied and is presented in Section 1.6. General conclusion is that selectivity and conversion depend much on the substituents adjacent to the ring. Fluorination using elemental fluorine of 2,4-dinitrotoluene, which we also used in this study, was attempted by Grakauskas (Figure 3.1).[54]

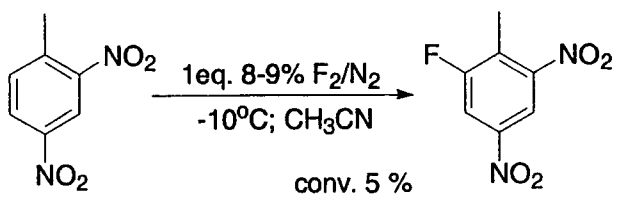


Figure 3.1

The Halogen-exchange reaction (Halex) is considered to be the most useful method for the synthesis of fluoroaromatic compounds in industry. By this method, halogen substituents of aromatic starting materials are exchanged by fluorine using alkali metal

fluorides (NaF, KF etc), silver fluoride and others. Since this reaction proceeds via a nucleophilic aromatic substitution, chlorine atoms are activated by electron-withdrawing groups such as $-NO_2$, -CN, -COX, $-CF_3$, etc. Mesomeric and inductive effects of those groups are most powerful when located in the *ortho-* or *para-* position (Figure 3.2).[2, 114, 115]

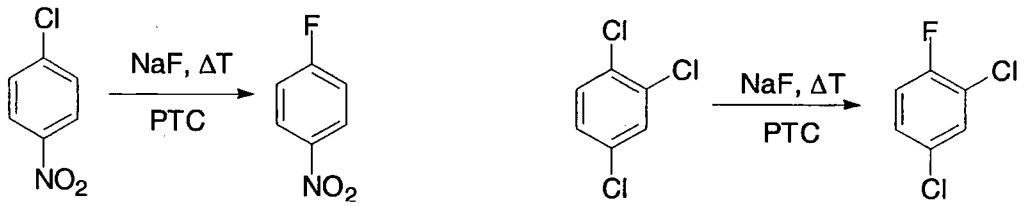
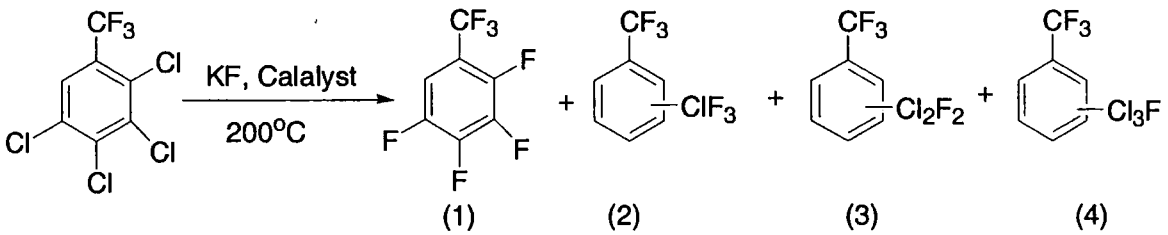
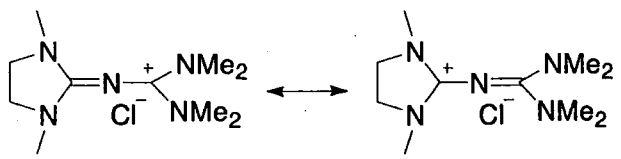


Figure 3.2

Recent advances in this methodology were achieved by use of catalysts which allowed reactions to proceed under milder temperatures and pressures.[10, 116] Pleschke and co-workers achieved a high selectivity and complete conversion of starting materials having two and more adjacent chlorines (Figure 3.3 and Table 3.1)



catalyst:



CNC$^+$ or PPh_4Br

Figure 3.3

Table 3.1 Conversions and distribution of the products in Halex reaction

Catalyst	Conv. (%)	(1)	(2)	(3)	(4)
CNC$^+$	100	84	17	0	0
PPh_4Br	100	1	6	78	14

Halex reactions were also employed for the fluorination of benzene chlorides with electron-donating groups. The reaction was facilitated using "disposable" substituent such as sulfonyl chloride, which sufficiently withdrew electrons from the ring so that the nucleophilic reaction can proceed (Figure 3.4).[117]

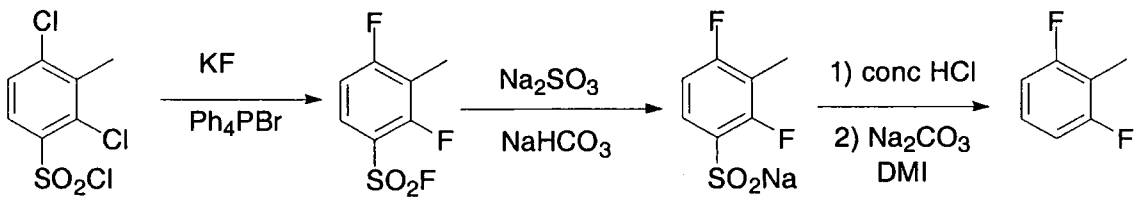


Figure 3.4

The reaction resulted in high regioselecitivity and good overall conversion (57%).

The Balz-Schieman reaction is one of the earliest developed methods for selective introduction of fluorine into aromatic molecules.

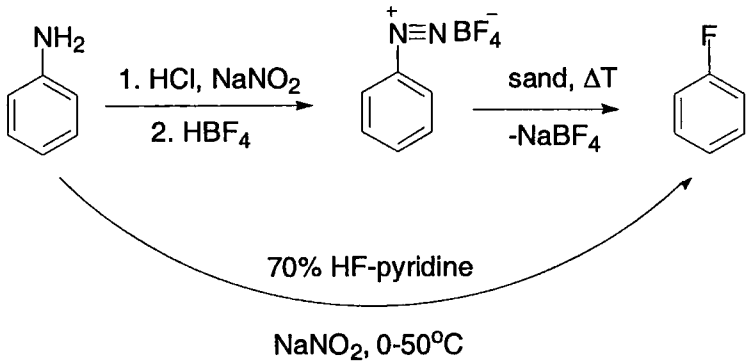


Figure 3.5

Arene diazonium tetrafluoroborate formed in the reaction was thermolyzed to give its monofluorinated analogue (Figure 3.5).[118] Although the reaction is quite efficient, scaling up is difficult due to the formation of the potentially explosive diazonium intermediate. The reaction can be the most conveniently controlled by diluting the reaction mixture using sea sand, which is a good inert medium. Recently, a more useful variant for technical applications was developed which involved *in-situ* formation of diazonium salt using 70% HF-pyridine with $NaNO_2$ which was subsequently thermolised to give the desired product.[119]

Reductive aromatization can be used for the synthesis of perfluorinated aromatics using perfluorinated saturated precursors. Since this method does not involve C-F bond formation it is not reviewed here in detail, but the reader is referred to the literature.[120-122]

In summary, we can conclude that the available fluorination methods usually involve substitution of other functional groups and often demand several steps in the synthesis. Methodology using elemental fluorine can avoid these disadvantages and allow direct synthesis of C-F bonds from C-H bonds.

3.2 Fluorination with elemental fluorine

3.2.1 2,4-Dinitrotoluene

Fluorination was carried out by passing 3 equivalents of fluorine through solution of 2,4-dinitrotoluene (**19**) in dry acetonitrile (Figure 3.6) which, according to the previous study, (Section 2.2.9.2), are the optimal conditions for the reaction.

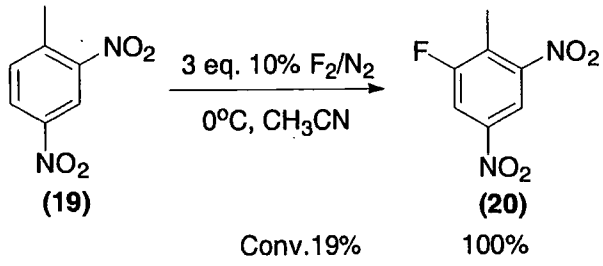


Figure 3.6

The ^{19}F NMR spectra of the crude product showed the presence of only one fluorinated product (Figure 3.6) in low conversion (19%).

After purification, the product was identified as 6-fluoro-2,4-dinitrotoluene (**20**) by comparison to the literature data.[54] In the ^{19}F NMR spectrum, there is a doublet at −106.1 ppm with a coupling constant of 8.9 Hz that agrees with $^{2}J_{HF}$ coupling with the *ortho*-proton attached to benzene ring. As a further proof of the structure a doublet at chemical shift 161.2 ppm in the ^{13}C NMR with the coupling constant 252.2 Hz was found, which is typical for fluorine-aromatic carbon $^{1}J_{CF}$ coupling. A doublet with a coupling constant 28.9

Hz, characteristic of two bond coupling between carbon and fluorine and chemical shift 114.6 ppm, corresponds to carbon bonded to the methyl group and indicates that fluorination occurs at the 6-position

2,4-Dinitrotoluene **(19)** was selected as a model substrate for optimisation, because it is a very cheap compound (£46 per 1 kg from Sigma Aldrich Co) and conversion can easily be determined using NMR spectroscopy. We investigated the effect of relative amounts of fluorine used in the reactions, the influence of solvent, temperature and concentration of the substrate. All results presented in the following tables are estimated according to ^{19}F NMR spectrum using fluorobenzene as a reference.

Ratio of Fluorine/ Substrate. Since 2,4-dinitrotoluene appears to be quite unreactive towards elemental fluorine, the reaction was carried out with an excess of fluorine (9 equivalents) under the same conditions: 0°C in dry acetonitrile. The main product is the monofluorinated derivative **(20)** and the conversion is improved up to 29% (Table 3.2, entry 2).

Table 3.2 Conversions during fluorination of 2,4-dinitrotoluene

Entry	Fluorine:Substrate ratio	Solvent	Temperature (°C)	Conv. (Yield) %
1	3	CH_3CN	0	19 (100)
2	9	CH_3CN	0	29 (100)

We consider that this is only a small improvement in conversion, considering a huge increase in the amount of fluorine was used.

Solvent and temperature survey. Many attempts to employ various solvents in order to optimise conditions of direct fluorination have been reported. Chambers and Moilliet demonstrated that solvents with higher acidity or permittivity can enhance direct fluorination for numerous disubstituted benzene derivatives acidic media results.[56, 123] It was also found that an increase in temperature can lead to an improvement in the conversion but often due to the existence of competing radical processes. Consequently, we reasoned that an acidic medium should be suitable for deactivated benzene derivatives, so we performed a solvent survey to establish the optimal reaction medium. Various temperatures were also examined, but only in sulfuric acid, because formic acid and acetonitrile tend to react with elemental fluorine at higher temperatures.

Acetonitrile. The initials experiments were performed in acetonitrile, resulting in a very clean reaction (Table 3.2). However conversion was very low, due to the deactivated nature of the substrate.

Table 3.3 Fluorination of 2,4-dinitrotoluene in different solvents

Entry	Fluorine:Substrate ratio	Solvent	Temperature (°C)	Conv. %
1	3	HCOOH	0	9
2	3	$HCOOH/CH_3CN$	0	9
3	3	H_2SO_4	-10	2
4	3	H_2SO_4	0	2
5	3	H_2SO_4	15	3

Formic acid. Direct fluorination of 2,4-dinitrotoluene **(19)** was carried out using formic acid as a solvent and gave a poor yield of monofluorinated product **(20)** (Table 3.3, entry 1). Although, the reaction is very clean and gave only one product, we did not conduct any further studies using this solvent, since we consider acetonitrile a better medium.

Formic acid/acetonitrile. The reaction using the mixture of formic acid and acetonitrile in a ratio 3:2 did not result in any improvements and only 9% of the starting material was converted into the monofluorinated derivatives **(20)** (Table 3.3, entry 2).

Sulfuric acid. Sulfuric acid is known as a useful solvent system which promotes electrophilic fluorination. However, the results obtained from fluorination in sulfuric acid (Table 3.3, entry 3, 4 and 5) show that 2,4-dinitrotoluene **(20)** cannot be transformed into fluorinated derivatives. Even increasing the temperature did not improve the yield and the starting material was almost completely recovered.

Concentration effects. The substrate has very low solubility in both, formic and sulfuric acid, so prepared solutions had at very low concentrations. A survey of various concentrations was conducted using mixtures of formic acid and acetonitrile in which

substrate solubility is higher than in formic acid itself, but the acidity retained. All experiments presented in Table 3.4 were carried out with 3 equivalents of fluorine at 0°C.

Table 3.4 Fluorination of 2,4-dinitrotoluene using different concentrations

Entry	Solvent	Concentration mol/dm^3	Conversion (Yield) %
1	CH_3CN / HCOOH (3/2)	0.04	9 (100)
2	CH_3CN / HCOOH (3/2)	0.1	19 (100)
3	CH_3CN	0.04	19 (100)
4	CH_3CN	0.2	20 (100)
5	CH_3CN	0.3	22 (100)

When a mixture of acetonitrile and formic acid was used as solvent medium, the reaction resulted in a slight increase of yield in the more concentrated solutions, (Table 3.4, entry 1 and 2). Acetonitrile allowed use of higher concentration of substrate (even 8 times) (Table 3.4, entry 5), but this did not alter the amount of 6-fluoro-2,4-dinitrotoluene **(20)** produced in the reaction.

We conclude that fluorination of 2,4-dinitrotoluene **(19)** results in a poor yield and gives only one product. The best conditions involve use of acetonitrile at 0°C. Variation of concentration did not give any improvement in conversion.

3.2.2 2,4-Dinitroanisole

Fluorination of 2,4-dinitroanisole **(21)** was performed using 3 equivalents of fluorine and it resulted in one product, 6-fluoro-2,4-dinitroanisole **(22),** in good conversion (55%).

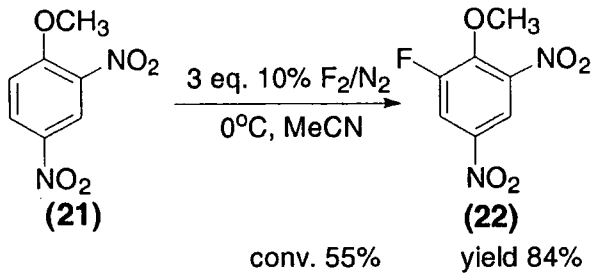


Figure 3.7

In the ^{1}H NMR spectra, H-5 proton was observed as a doublet of doublets with a coupling constant 10.4 Hz which is typical for three bonds H-F coupling (2.4 Hz) with an adjacent proton. The ^{13}C NMR spectrum is particularly helpful in determination of the structure of the product. Resonance with chemical shift of δ_C=147.1 ppm was found to be the doublet of 13.5 Hz, which is literary the same as for butoxy derivatives, indicate carbon with attached methoxy-group Therefore, we can conclude that fluorination occurred at 6-position.

It is interesting to note that the total yield of the product is lower compared to butoxy-derivative, although both substituents posses similar inductive and resonance effects. However, the reaction is regioselective and consistent with an electrophilic process.

3.2.3 2,4–Dinitroacetanilide

We decided to extend this methodology of fluorination to other 2,4-dinitro-benzene derivatives bearing an electron-donating group. Beside alkoxy and alkyl groups, nitrogen substituents are also considered as good electron-donating substituents. Fluorination of 2,4-dinitroaniline was not attempted, since it can be predicted that fluorination will proceed at nitrogen of the amino group to give N-fluoroderivatives. Fluorination of amines has already been reported in many earlier studies.[66, 124] We decided to use an acetanilide derivative to assess reactivity with elemental fluorine. Since 2,4-dinitroacetanilide is not available, we synthesised it from 2,4-dinitroaniline.

3.2.3.1 Synthesis of 2,4-dinitroacetanilide

2,4-Dinitroacetanilide (**24**) was synthesised from commercially available 2,4-dinitroaniline. Acetic anhydride was added to 2,4-dinitroaniline (**23**), which was dissolved in glacial acetic acid.

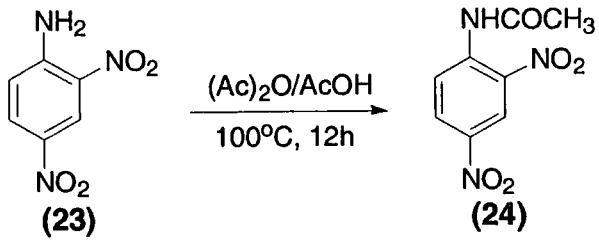


Figure 3.8

The reaction mixture was refluxed for 12 h, the crude product was purified by recrystalisation and the structure was confirmed by X-ray crystallography to give undisputable proof of product structure (Figure 3.9).

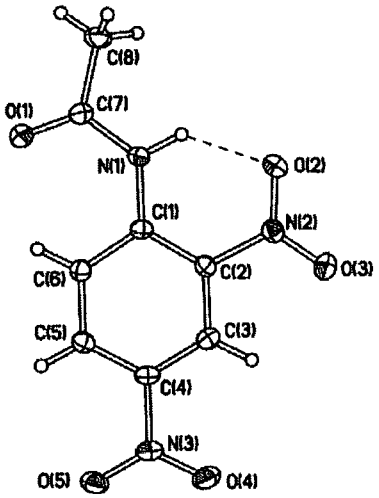
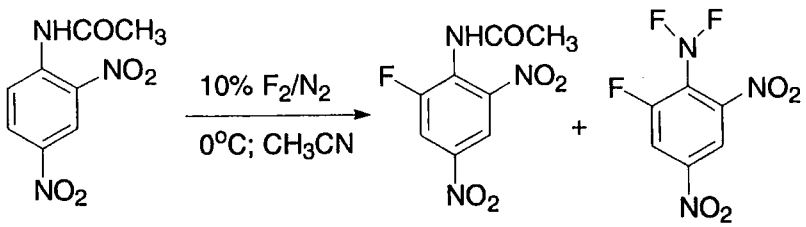


Figure 3.9

The isolated pure product was used in fluorination studies.

3.2.3.2 Fluorination of 2, 4-dinitroacetanilide

Fluorination of 2,4-dinitroacetinilide **(24)** (Figure 3.10) was carried out by passing 3 equivalents of elemental fluorine through a solution.



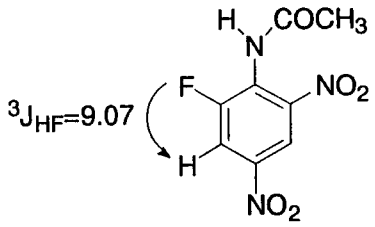
(24) **(25)** **(26)**

conv. 22% 64% 14%

Figure 3.10

Analysis of the crude product shows that two main products were formed: 5-fluoro-2,4-dinitroacetanilide **(25)** and 5-fluoro-N,N-difluoro-2,4-dinitroaniline **(26)** in ratio 10:1.5. The conversion, as estimated by ^{19} F NMR, was 22%.

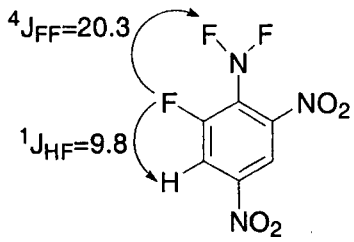
5-Fluoro-2,4-dinitroacetonilide **(25)** (Figure 3.11) was identified from analysis of the crude mixture, but isolation of this product proved to be very difficult.



δ=107.5 ppm (d, F-C6)

Figure 3.11

The only isolated product was 5-fluoro-N,N-difluoro-2,4-dinitroaniline and structure was confirmed by comparison to the literature data.[125] These classes of compounds have high energy density, so they found application as explosives, detonators, or as components in explosive and propellant compositions.[126] There are several reports on the synthesis of N,N-difluoroanilines, which involves fluorination of nitroanilines using CF_3OF in MeOH-CH_2Cl_2[127] or using liquid HF as fluorinating agent in acetonitrile.[125]



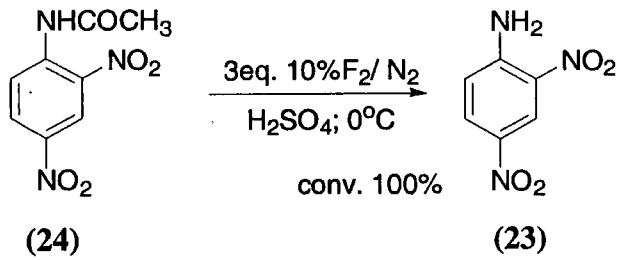
δ: 63.05 ppm (d, 2F, NF_2),

δ: −109.4ppm (dt, 1F, *F*-C6)

Figure 3.12

Two resonances, in the ^{19} F NMR spectra in a ratio 2:1, indicate multiple fluorination and ^{1}H NMR shows only chemical shifts at 8.4 ppm and 8.3 ppm. Other products were detected by ^{19}F NMR and GC-MS but could not be identified.

Fluorination of 2,4-dinitroacetanilide **(24)** was attempted in sulfuric acid (Figure 3.13) .



(24) **(23)**

Figure 3.13

However, acid promoted deacetylation of acetanilide led to the formation of 2,4-dinitroaniline **(23)**.

We conclude that fluorination of 2,4-dinitro-acetanilide **(24)** results with very poor conversion and a lack of regioselectivity. Further study was not conducted as it is found that the substrate is unsuitable for this methodology.

3.2.4 1-Chloro-2,4-dinitro-benzene

Fluorination of 1-chloro-2,4-dinitro-benzene (**27**) using 4 equivalents of elemental fluorine gave the expected product, 1-chloro-6-fluoro-2,4-dinitrobenzene (**28**), in good conversion (45%) and high yield.

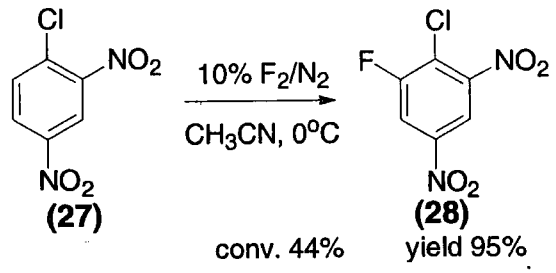


Figure 3.14

In the ^{19}F NMR spectrum of the pure product, a doublet with chemical shift at -103.2 ppm and coupling constant of 7.8 Hz was found, which is in agreement with three bonds hydrogen fluorine coupling. In the ^{13}C NMR, C-1 was assigned as a doublet with 21.8 Hz, typical for two bonds coupling with *ortho*-substituted fluorine. The carbons C-2 and C-4 with attached nitro groups both show as a doublet with typical three bonds coupling. Assignment of each (C-2 and C-4) was conducted by comparison to the starting material, where C-2 is shifted up-field due to the neighbouring carbon with attached chlorine.

In conclusion, fluorination of 1-chloro-2,4-dinitro-benzene (**27**) proceeds, fluorination of the previously described substrates at the *ortho*-position to the chlorine and *meta*- to both the nitro groups, consistent with an electrophilic process. We found that introduction of chlorine, as a substituent, in the substrate increases conversion into monofluorinated product (**28**) in comparison to the model compound bearing a methyl group.

3.2.5. 1-Fluoro-2,4-dinitro-benzene

Fluorination of 1-fluoro-2,4-dinitro-benzene (**29**) using 4 equivalents of elemental fluorine resulted in formation of 1,6-difluoro-2,4-dinitro-benzene (**30**) with 16% conversion.

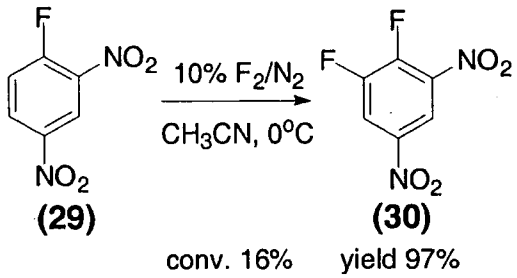


Figure 3.15

In the ^{19}F NMR spectrum, we found doublet of doublets with chemical shift at −126.0 pm and doublet of triplets at −129.0 ppm in ratio 1:1, which implies that two fluorines are positioned next to each other. The ^{13}C NMR contains two doublets of doublets each with one bond coupling constants (259.1 Hz and 278.3 Hz) and two bond coupling constants (13.2 Hz and 15.7 Hz) which indicates presence of two fluorines attached to the neighboring carbons.

As expected, 1-fluoro-2,4-dinitrobenezene **(29)** is more deactivated towards electrophilic substitution than 1-chloro-2,4-dinitrobenezene **(27),** and therefore, the reaction resulted in lower conversion .

3.2.6 1,3-Dinitro-benzene

The reaction was carried out using 5 equivalents of fluorine and 1,3-dinitro-benzene **(31)** in dry acetonitrile (Figure 15.). After isolation of the crude product, ^{19}F NMR showed only one peak (triplet) with chemical shift at −103.6 ppm.

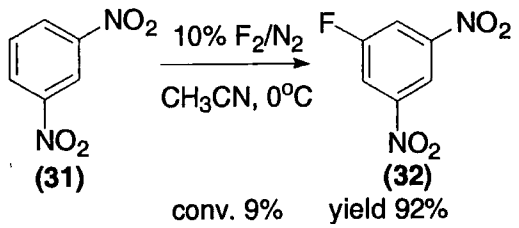


Figure 3.16

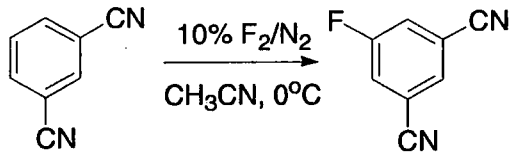
The isolated product is 1-fluoro-3,5-dinitrotoluene **(32)**. As expected, fluorination occurred in the *meta*-position, which is consistent with an electrophilic substitution process. Due to the symmetry of the molecule, in the ^{13}C NMR spectrum there is one signal with two bond fluorine-carbon coupling (115.1 ppm, $^{2}J_{CF}$=28.9 Hz) and it appears as a high intensity doublet, characteristic of non-substituted carbon at an *ortho*-position to the fluorinated carbon.

In summary, the reaction resulted was in only one product, but in low conversion due to the deactivating nature of the substituents.

3.2.7 1,3-Dicyano-benzene (Isophthalonitrile)

We decided to extend this methodology to other deactivated benzene derivatives such as benzonitriles and to examine relative reactivity to nitroderivatives.

Fluorination of 1,3-dicyano-benzene **(33)** was carried out using both 3 and 9 equivalents of fluorine (Figure 3.17) in acetonitrile. Characterisation of the crude product by GC/MS confirmed the presence of one main monofluorinated product **(34)**. According to the ^{19}F NMR spectra, conversions were estimated in both cases (Table 3.5, entry 1 and 2) to be almost the same (10% and 12%), but regioselectivity was slightly lower when 9 equivalents of elemental fluorine were used (Table 3.5).



(33) **(34)**

Figure 3.17

Table 3.5 Fluorination of 1,3-dicyano-benzene using different relative amount of fluorine

Entry	Fluorine: Substrate ratio	Solvent	Temperature (°C)	Conv. (Yield) %
1	3	CH_3CN	0	10 (80)
2	9	CH_3CN	0	12 (72)

Separation of the product from the starting material was very difficult due to their similar polarities and boiling points, but also due to the low conversion. Purification of the sample allowed characterization of the product by ^{1}H NMR, where we can see two peaks in ratio 2:1. In the ^{19}F NMR peak at −105.7 ppm, triplet with coupling constant 6.9 Hz and corresponds to fluorine attached to the aromatic ring.

According to our study we conclude that fluorination of 1,3-dicyano-benzene **(33)** results in high selectivity and is consistent with an electrophilic aromatic substitution process.

3.2.8 3-Nitrobenzonitrile

We demonstrated that fluorination of 1,3-dicyano-benzene and 1,3-dinitro-benzene in dry acetonitrile provide only one product but in a low conversion. The direct fluorination of 3-nitrobenzonitrile **(35)** using 3 equivalents of fluorine was performed in dry acetonitrile and conversion was found to be 14% (Figure 3.18). The ^{19}F NMR spectrum of the crude product showed the presence of only one product which was subsequently identified as 5-fluoro-3-nitrobenzonitrile **(36),** by comparison to the literature data.[128]

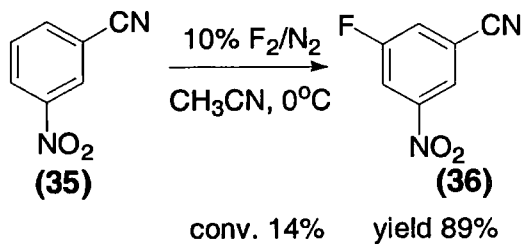


Figure 3.18

The complete evidence that fluorination occurred in the *meta*-position to both substituents was gained from the ^{13}C NMR spectrum, where two doublets with coupling constants of 5.7 Hz and 7.8 Hz, a characteristic of bonds C-F couplings, are as signed as C-1 (carbon with attached cyano-group) and C-3 (carbon with attached nitro-group), respectively.

Fluorination was attempted in sulfuric acid to ascertain whether acetonitrile is the only suitable medium but the reaction did not result in any fluorination. Only a negligible amount of non-fluorinated products was observed as result of acid promoted hydrolysis.

However, we conclude that the only suitable solvents for fluorination of cyanobenzene derivatives are non-acidic polar solvents. We found that fluorination of 3-nitrobenzonitrile **(35)** is possible using elemental fluorine. The reaction is very clean and is consistent with an electrophilic process, but proceeds in very low conversion.

3.3 Fluorination with Selectfluor™

3.3.1 2,4-Dinitrotoluene

Fluorination of 2,4-dinitrotoluene **(19)** using Selectfluor™ was carried out in dry acetonitrile at reflux temperature for 18 h (Figure 14.) to compare fluorination methods.

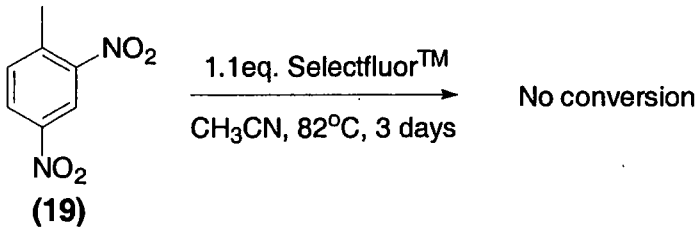


Figure 3.19

The ^{19}F NMR and GC showed the presence of starting material only. We can conclude that Selectfluor™ is a less reactive reagent that elemental fluorine in reaction with benzene derivatives bearing EWG-substituents.

3.4 Discussion of the reaction mechanism

According to the obtained results, the reactions with most of the substrates proceed via a selective, electrophilic process. Regioselectivity is mainly achieved due to the presence of deactivated groups: (-NO_2 and CN).

When strongly activating substituents are introduced into the molecule, fluorination proceeds in high conversion for butoxy- and moderately for methoxy- substituent.

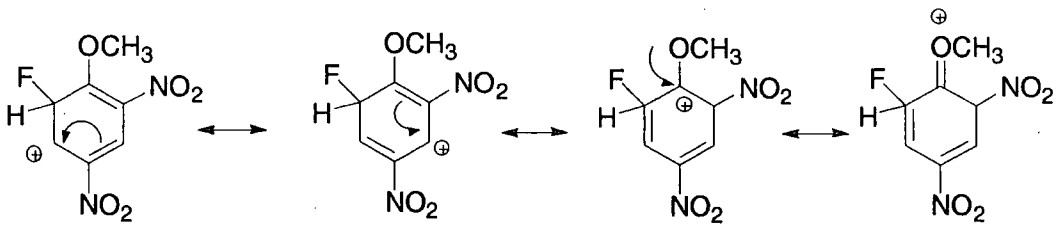


Figure 3.20

In the mechanism shown in the Figure 3.20, the intermediate is stabilized by four resonance forms. *Meta*-positions to the alkoxy-substituents are additionally deactivated by two nitro groups.

$NHCOCH_3$ is considered as a moderately activating substituent, but a resonance effect that directs electrons away from the ring is also present (Figure 3.21).

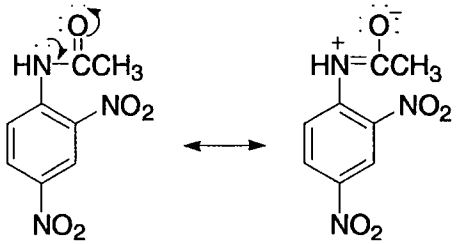


Figure 3.21

The withdrawing effect of $-NHCOCH_3$ is probably the reason why fluorination results in a very low conversion.

When a methyl group is present in the molecule, the reaction proceeds in poor conversion, even though various conditions were attempted. Halogens are considered to be weakly deactivating substituents, but chlorine activates the ring towards fluorination and the reaction proceeds in moderate conversion. The C-Cl bond is strongly polarized and $\delta+$ on carbon acts to retard substitution (Figure 3.22, a).

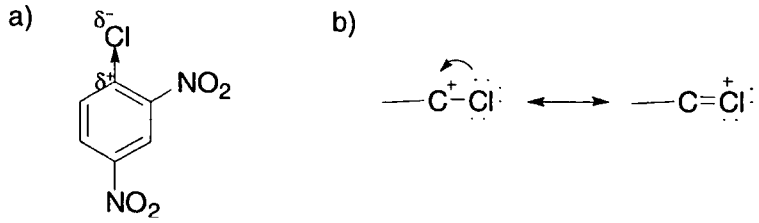


Figure 3.22

However, there is also a resonance effect that can help to stabilize the intermediate in a case of *ortho*-substitution (Figure 3.22, b).

3.5 Conclusions

Fluorination of highly deactivated aromatic compounds using elemental fluorine was possible and found to be very selective, in many cases yielding only one product. Conversions can be regulated by variation of the substituent and relative amount of elemental fluorine applied.

Despite it being suggested in the past that fluorination of aromatic compounds using elemental fluorine gives the best results in the acidic environment, reaction of 2,4-dinitrotoluene in sulfuric acid do not proceed even at higher temperatures. Acetonitrile was found to be the best solvent for fluorination of the deactivated substrates. The best result regarding conversion was achieved with substrates bearing alkoxy-substituents and the chlorine-substituted derivative.

The deactivated aromatic compounds do not undergo fluorination using Selectfluor™.

Chapter 4 Fluorination of benzaldehyde derivatives

4.1. Introduction

As a continuation of our previous study concerned with fluorination of deactivated benzene derivatives, this chapter presents a study of the reactivity of 1,3 and 1,4 di-substituted systems, bearing at least one aldehyde group, towards elemental fluorine. Solvents can often affect the distribution of products formed, so their effect in the studied systems is also presented. Furthermore, the efficiencies of the commercially available fluorinating agent Selectfluor™ and elemental fluorine were also compared.

A short literature overview, presenting the most important routes for the synthesis of fluorinated benzaldehydes, is given in Section 4.1.1 and is followed by a discussion of the present work.

4.1.1 Synthesis of fluorinated benzaldehyde derivatives

Fluorinated benzaldehydes are important building blocks for various pharmaceuticals, cosmetic products, polymer additives and flavourings.[129-132] There is a huge demand for economically viable routes to these types of compounds and several synthetic routes have been already developed. Most methods used for the fluorination of benzene derivatives (Section 3.1.1) can be applied to benzaldehyde derivatives also.

Electrophilic fluorination of several benzaldehyde derivatives was achieved using elemental fluorine in sulfuric acid[123] resulting in the main product fluorinated at 2-position (Figure 4.1).

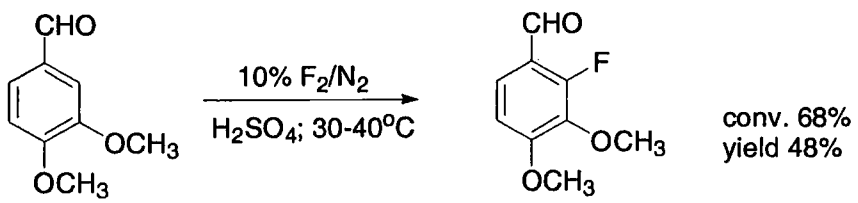


Figure 4.1

This method is limited to the benzaldehyde substrates having a moiety with a lone pair of electrons (such as –OH, –OR) adjacent to the aromatic ring. Fluorination of 4-methoxybenzaldehyde was performed in sulfuric and formic acid (Table 4.1), but selectivity was achieved only in sulfuric acid.

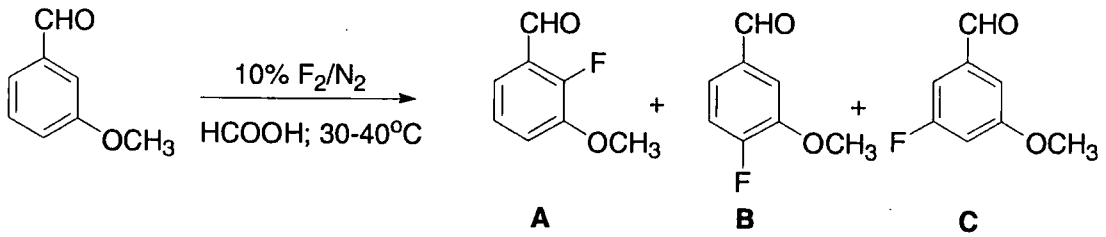
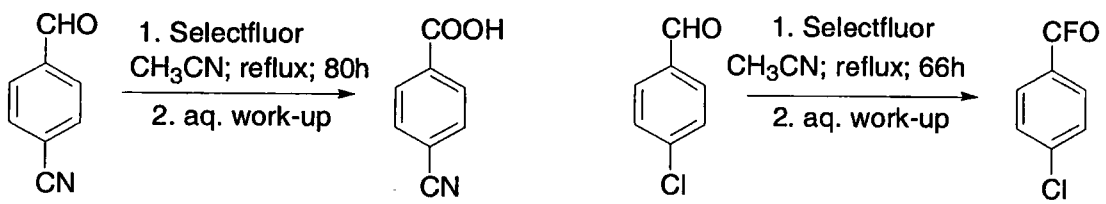


Figure 4.2

Table 4.1 Fluorination of 4-methoxybenzaldehyde using elemental fluorine

Entry	Solvent	Conv. (%)	Yield A (%)	Yield B (%)	Yield C (%)
1	H_2SO_4	50	98	trace	trace
2	HCOOH		60	22	19

In the reaction with Selectfluor™, 1,4-substituted benzaldehydes oxidized to their acid analogues (Figure 4.3, a) and the reaction proceeded via formation of benzoyl fluorides.[68]



(a) (b)

Figure 4.3

Benzoyl fluorides turned out to be very unstable in the presence of any moisture. Thus they were hydrolysed during the aqueous work-up procedure. The only exception was found to be 4-chlorobenzoyl fluoride (Figure 4.3, b) possessing sufficient stability to be isolated.

Caesium fluoroxysulfate and xenon fluoride, usually considered to be electrophilic reagents, were used for fluorination of benzaldehyde and details of this study were presented in Section 1.8.2 and 1.9.

Nucleophilic reagents. One of the most commonly used methods for the synthesis of fluorinated benzaldehydes is the Halex reaction. It is based on the nucleophilic substitution of chlorine by fluorine and has a long history of application.[23, 133, 134] Recent developments involve the use of potassium fluoride, tetra-phenyl-phosphonium bromide and catalysts (Figure 4.4, Table 4.2).[116]

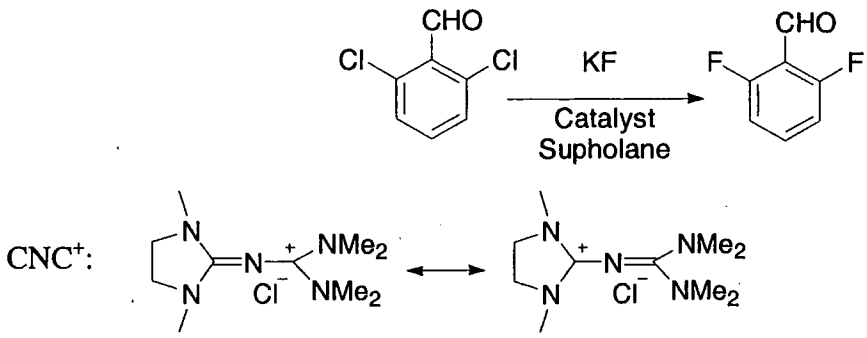


Figure 4.4

Table 4.2 Halex-fluorination of benzaldehydes using various catalysts

Entry	Catalyst (mol%)	Temperature (°C)	Time (h)	Yield (%) (Conversion (%))
1	PPh_4Br (2.5)	180	24	72 (100)
2	CNC^+ (2.5)	180	24	63 (100)
3	$(NEt_2)PNPh_3Br$ (2.5)	180	24	54 (100)
4	$(Et_2N)_2NPBr$/ $C_2H_5O((C_2H_4O)_n)NMe_3Cl$ (6)	165	20	69 (100)

It was concluded that the best catalyst for fluorination of 2,6-chlorobenzaldehyde was PPh_4Br (Table 4.2, entry 1) since the catalysts CNC^+ and PNP^+ tend to decompose during reaction (Table 4.2, entry 2 and 3). The outcome of fluorination of other benzene derivatives shows a better catalytic activity of CNC^+ (Section 3.1.1), so it was concluded that there are no universal rules for running successful Halex reactions. Therefore, the reaction conditions have to be chosen for each reaction individually.

Nucleophilic fluorination methods provide the aromatic systems with fluorine at different positions with respect to the other substituents, than those prepared by an

electrophilic process. Therefore, it would be useful to develop a method for the fluorination of benzaldehyde and its derivatives by elemental fluorine via an electrophilic substitution.

Other methods that employ transformation of functional group of already fluorinated analogues are very efficient routes to fluorinated benzaldehydes derivatives. Since they are not of great interest for this study, they are not discussed here, but the reader is directed to the literature.[132]

4.2 Fluorination of benzaldehyde and its derivatives using elemental fluorine

4.2.1 Benzaldehyde

Direct fluorination of benzaldehyde with 3 equivalents of fluorine was performed in acetonitrile at 0°C. According to the ^{19}F NMR data, we found that the reaction resulted in 48% conversion and 4 products were formed. These products were subsequently identified as 2-fluorobenzaldehyde **(38)**, 3-fluorobenzaldehyde **(39)**, 4-fluorobenzaldehyde **(40)** and benzoyl fluoride **(41)** in the ratio 0.9:5.2:1.9:1, respectively.

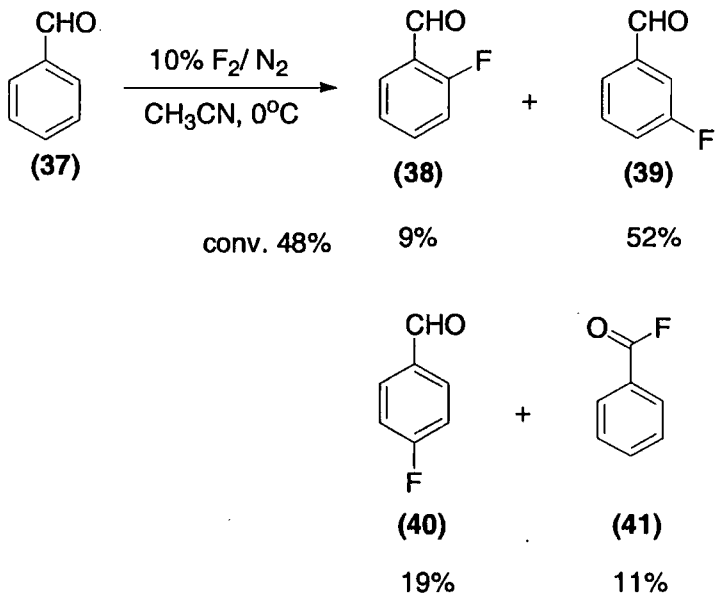
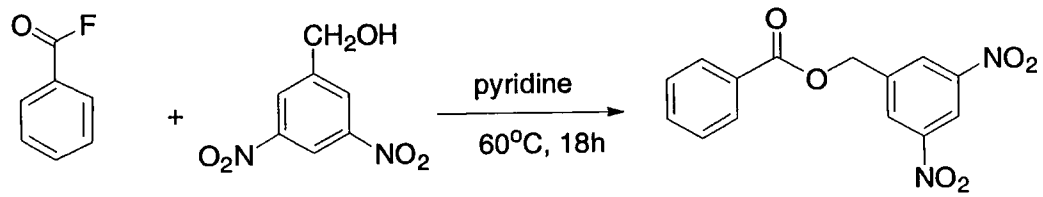


Figure 4.5

Products **(38)**, **(39)** and **(40)** were identified by comparison with literature data.[130, 135] Their isolation was very difficult owing to their instability, similar boiling points and

polarity, which eliminates distillation or preparative gas chromatography as potential methods for purification.

Benzoyl fluoride was detected in the ^{19}F NMR spectrum of the reaction mixture as a resonance at 20.3 ppm. When a standard aqueous work-up procedure was applied, loss of the benzoyl fluorides was detected by ^{19}F NMR in the crude product. The instability of benzoyl fluorides has already been reported.[68] It easily reacts with nucleophiles, therefore it is likely that **(41)** reacted with water during aqueous work-up procedure to give benzoic acid or other by-products.



(41) **(42)** **(43)**

Figure 4.6

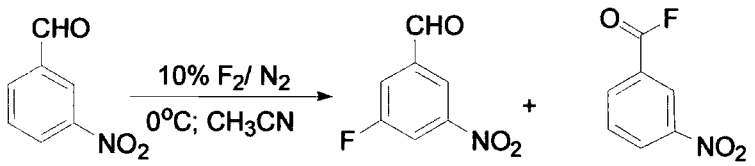
We decided to isolate benzoyl fluoride **(41)** in the form of an ester, since it can be easily separated from the rest of the mixture. When fluorination with elemental fluorine was completed, 3,5-dinitro-benzyl alcohol **(42)** was added to the reaction mixture. The reaction was catalyzed by a small amount of pyridine and monitored by ^{19}F NMR until completion of the reaction.

3,5-Dinitro-benzyl benzoate **(43)** was separated from the mixture by recrystalization and the structure was confirmed by NMR spectroscopy. In the ^{1}H NMR spectra, the singlet of 5.56 ppm was assigned to $-CH_2-$, which is typical for a methylene group attached to a carboxylic group. Further evidence of the structure was gained from the ^{13}C NMR, where the carbonyl carbon was found at 166.1 ppm, which is typical for an ester group.

We can conclude that benzaldehyde does not react selectively with elemental fluorine and that the reaction proceeds at all possible positions in the molecule. The *meta*-position is favoured, which is in agreement with electrophilic fluorination.

4.2.2 3-Nitrobenzaldehyde

Fluorination of 3-nitrobezaldehyde **(44)** was carried out following a similar procedure to that in the previous experiment in acetonitrile, and resulted in 39% conversion (Figure 4.7). The major products obtained from the reaction were 5-fluoro-3-nitrobenzaldehyde **(45)** and 3-nitrobenzoyl fluoride **(46),** in the ratio 1:4.1 according to the ^{19}F NMR spectrum of the reaction mixture.



(44) conv. 39% **(45)** 19% **(46)** 79%

Figure 4.7

The product **(45)** was isolated pure and characterised fully by X-ray crystallography. (Figure 4.8)

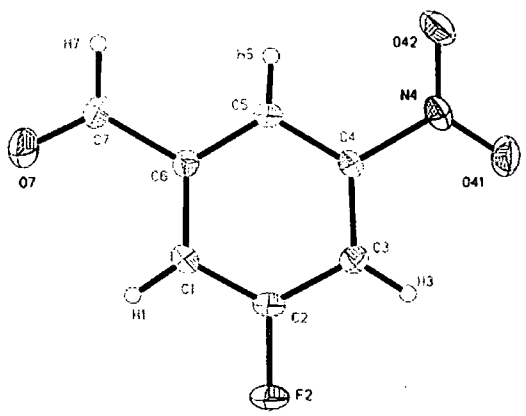
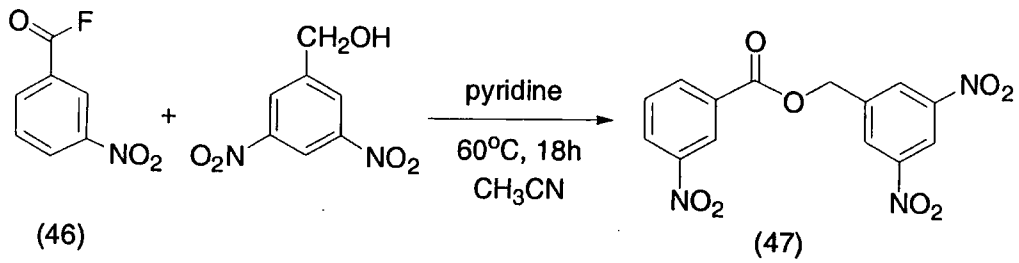


Figure 4.8

According to the crystal data, fluorine has formed intermolecular hydrogen bond length 2.5 Å.

The other product formed alongside **(45)** was 3-nitro-benzoyl fluoride **(46),** observed in the ^{19}F NMR spectrum at 20.8 ppm. This product **(46)** was isolated after

esterification with 3,5-dinitro-benzyl alcohol (Figure 4.9) in the presence of base (pyridine), which catalyzed the reaction analogously as in the previous example (Figure 4.6). The reaction was monitored by ^{19}F NMR and ran until complete conversion to the ester was achieved.



(46) (47)

Figure 4.9

Confirmation of the structure of 3,5-dinitrobenzyl 3-nitro-benzoate was obtained by ^{1}H NMR. Six signals were found corresponding to the aromatic protons and one signal at 5.79 ppm attributed to the $-CH_2-$ group. The substitution of fluorine with oxygen resulted in a shifting of the carbonyl carbon signal in ^{13}C NMR from 190 ppm (CFO) to 164 ppm, characteristic of carbonyl in ester group.

Table 4.3 Direct fluorination of 3-nitro-bezaldehyde in different solvents

Entry	Fluorine: substrate ratio	Solvent	Temperature (°C)	Conv. ^{19}F NMR. (%)	Ratio **45:46**
1.	3	CH_3CN/ HCOOH	0	36	1:2.9
2.	3	HCOOH	0	21	1:1.1
3.	3	H_2SO_4	15	>1	n/a

Mixture Acetonitrile/Formic acid. Direct fluorination of **(44)** was performed in acetonitrile/formic acid and resulted in 36% conversion. It is worth noting that the distribution of the products was altered and less benzoyl fluoride was produced (Table 4.3, entry 1).

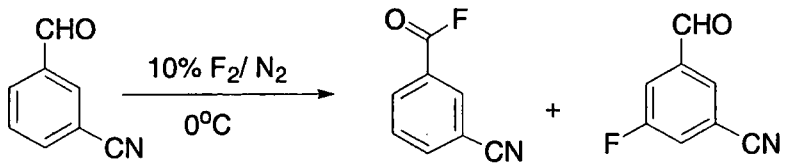
Formic acid. Direct fluorination of 3-nitro-benzladehyde **(44)** in formic acid resulted in significantly lower conversion (Table 4.3, entry 2). The same products, **(45)** and **(46),** were produced in the reaction, but distribution of these products was different from the previous two cases. The ratio of 3-nitro-benzoyl fluoride to 5-fluoro-3-nitro-benzaldehyde was 1:1.1, according to the ^{19}F NMR spectra of the reaction mixture.

Sulfuric acid. Direct fluorination of **(44)** in sulfuric acid was almost completely suppressed (Table 4.3, entry 3) even at a higher temperature (15°C). Repeating experiments using a greater excess of fluorine resulted in a very similar conversion, so consequently, it was concluded that sulfuric acid is not a suitable medium for fluorination.

In summary, we found that fluorination of 3-nitro-benzaldehyde **(44)** proceeds at two reactive sites, the carbonyl group and the aromatic ring. Substitution at the aromatic ring is consistent with an electrophilic process. The solvent enabling the highest conversion was acetonitrile, while the acidic medium suppresses the reaction slightly at the carbonyl group and consequently results in a lower conversion. The mechanism of the fluorination is discussed later in this chapter.

4.2.3 3-Formylbenzonitrile

We initially performed the direct fluorination of 3-formylbenzonitrile (Table 4.4, entry 1) with 3 equivalents of fluorine in dry acetonitrile. The ^{19}F NMR spectrum of the reaction mixture showed the presence of two main components, which were subsequently identified as 5-fluoro-3-formyl-benzonitrile **(49)** and 3-cyano-benzoyl fluoride **(50)** in the ratio 1:3.2 and 34% conversion of starting material was obtained.



(48) **(49)** **(50)**

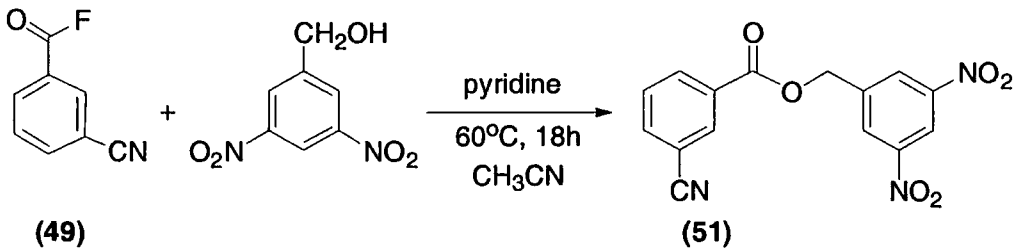
Figure 4.10

Table 4.4 Direct fluorination of 3-formyl-benzonitrile in different solvents

Entry	Fluorine: Substrate ratio	Solvent	Temperature (°C)	Conv. (%)	Yield (**49**) (%)	Yield (**50**) (%)
1.	3	MeCN	0	34	23	75
2.	3	HCOOH	15	36	41	50

In the ^{19}F NMR of the product (**50**), a triplet at −107.2 ppm with a coupling constant 7.2 Hz was found implying that substitution had occurred at the 5-position (Figure 4.10). The presence of resonances that correlate to three aromatic protons in the ^{1}H NMR spectra indicates that fluorination occurred on the benzene ring.

The confirmation of the structure of 3-cyano-benzoyl fluoride was made after esterification with 2,3-dinitro-benzyl alcohol in the presence of a base (pyridine), analogously to the nitro-derivative.



(49) **(51)**

Figure 4.11

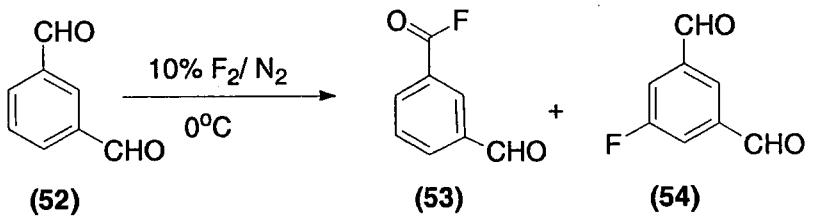
The disappearance of the peak at 18.7 ppm in the ^{19}F NMR spectra of the crude mixture proved complete substitution of fluorine attached to the carbonyl group (Figure 4.11). Therefore reaction resulted in the formation of 3,5-dinitro-benzyl-3-cyano-benzoate (**51**). The compound (**51**) was identified by NMR spectra and it is the analogous product of esterification of 3-nitro-benzoyl fluoride. Additionally, in the ^{13}C NMR spectra, the resonance at 117.3 ppm corresponds to the carbon from CN-group, while the C-3 carbon bearing the −CN group is shifted down-field, compared to C-3 from the analogous compound (**47**).

Direct fluorination of (**48**) in formic acid resulted in a conversion of 36%, but more of the ring-fluorinated product was produced and consequently, the distribution of products was altered.

We found that fluorination of 3-cyano-benzladehyde (**48**) proceeds in low conversion and at both the carbonyl group and benzene ring, similar to the previous example (**46**). However, the distribution of products in these two reactions is different, although they were performed under the same conditions. This is probably caused by the different effect of $-NO_2$ and –CN substituents on the benzene ring.

4.2.4 Isophthalaldehyde

The direct fluorination of isophthalaldehyde (**52**) with 3 equivalents of fluorine resulted in 22% conversion (Figure 4.12). The ^{19}F NMR spectrum of the crude product showed the presence of two major products in proportions of 1:1.6. These products were subsequently identified as 5-fluoroisophthalaldehyde (**53**) and monofluoro-isophthalate (**54**), respectively. Only a trace of the difluoro-isophthalate was detected.



(52) (53) (54)

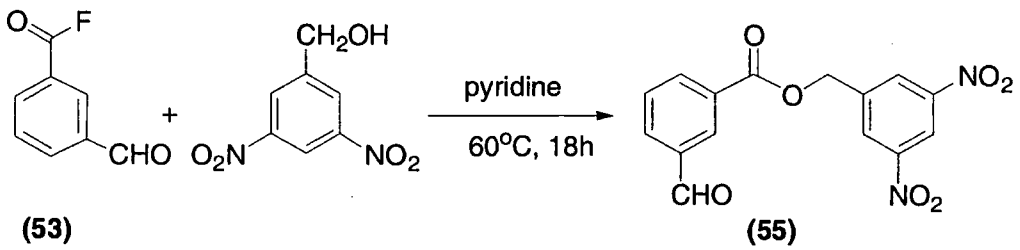
Figure 4.12

Table 4.5 Direct fluorination of isophthalaldehyde in different solvents

Entry	Fluorine: Substrate ratio	Solvent	Temperature (°C)	Conv. (%) (ratio **53:54**)
1	3	MeCN	0	16 (1: 1.6)
2	3	H_2SO_4	15	<1

Identification of the main product, 5-fluoro-isophthalaldehyde (**54**), was made by comparison of the ^{19}F NMR and ^{1}H NMR to literature data.[136] The fluorination is consistent with an electrophilic mechanism and substitution is directed into the *meta*-position with respect to both aldehyde groups.

The second product, benzoyl fluoride derivative **(55),** was transformed to the ester **(55)** using previously established conditions (Figure 4.13).



(53) **(55)**

Figure 4.13

Fluorination was also attempted in sulfuric acid at a higher temperature (15-18°C) (Table 4.5, entry 2). Despite the fact that the best dielectric characteristics and pK_a belongs to sulfuric acid, fluorination effectively does not proceed. A possible reason could be protonation of the carbonyl group, which causes deactivation of both possible positions for fluorination (ring and carbonyl group).

We found that direct fluorination of the isophthalaldehyde proceeds with a lower conversion in comparison to the previous analogues. Although, the molecule has two carbonyl groups, the reaction proceeds only at one.

4.2.5 3-Trifluoromethyl-benzaldehyde

Direct fluorination of 3-trifluoromethyl-benzaldehyde **(56)** with 3 equivalents of fluorine resulted in 38% conversion and the formation of two major products (Figure 4.14), which were identified as 5-fluoro-3-trifluoromethyl-benzaldehyde **(57)** and 3-trifluoromethyl-l-benzoyl fluoride **(58),** in a ratio 1:1.8.

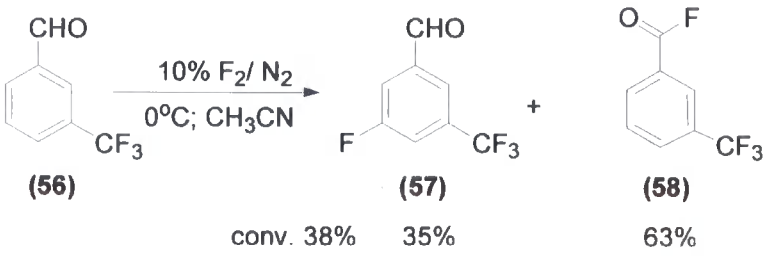


Figure 4.14

The pure product **(57)** was isolated and its structure was confirmed by comparison to an authentic sample from Sigma Aldrich. In the ^{19}F NMR spectrum, two resonances at chemical shifts of −63.4 ppm and −110.7 ppm (ratio 3:1), correlate to the fluorine from $-CF_3$ and the fluorine attached to the ring, respectively. The main product **(58)** was isolated after esterification with 3,5-dinitrobenzyl alcohol (Figure 4.16).

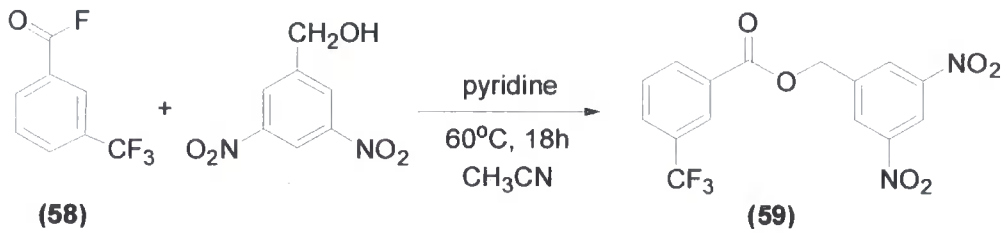


Figure 4.15

The reaction was monitored until completion and the pure ester **(59)** was isolated by simple recrystalisation from methanol. This product was isolated in the form of white crystals and its structure was confirmed by X-ray crystallography (Figure 4.16).

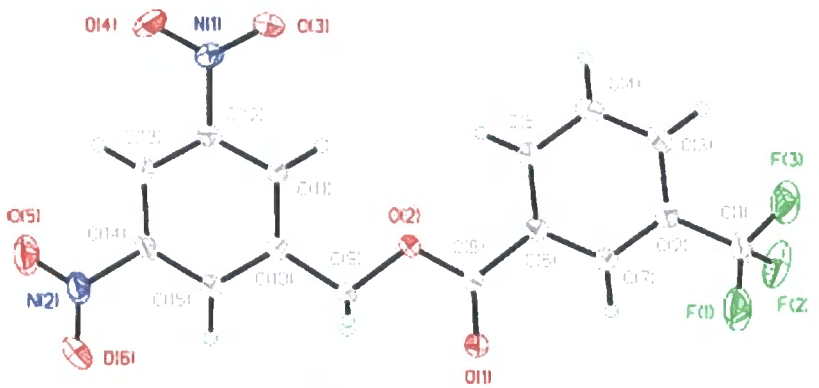
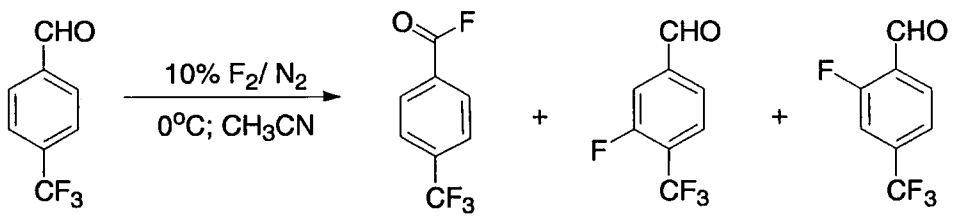


Figure 4.16

We found that 3-trifluoromethyl-benzaldehyde reacts with elemental fluorine in similar manner to other benzaldehyde analogues to give two main products, **(57)** and **(58)**. It is worth noting that the product distribution is different compared to the previous benzaldehyde derivatives, and is closest to the cyano-derivatives.

4.2.6 4-Trifluoromethylbenzaldehyde

The direct fluorination of 4-trifluoromethyl-benzaldehyde **(60)** with 3 equivalents of fluorine resulted in 38% conversion (Figure 4.17, Table 4.6). The ^{19}F NMR spectrum of the crude product showed the presence of two major products, 5-fluoro-4-trifluoromethyl-benzaldehyde **(62)** and 4-trifluoromethyl-benzoyl fluoride **(61)** in proportions of 2:1, which were subsequently identified by comparison to the literature data.[101]

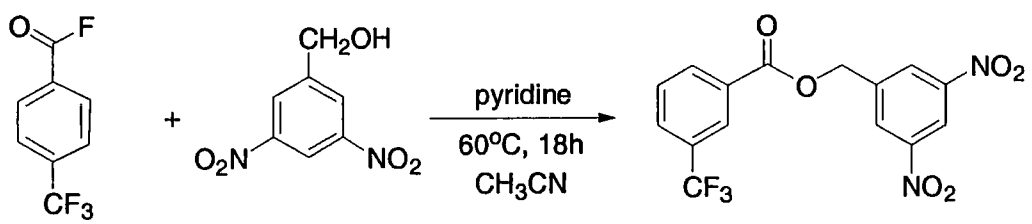


(60) **(61)** **(62)** **(63)**

conv.38% 51% 25% 9%

Figure 4.17

After 7 hours of reflux in the presence of pyridine (Figure 4.18), ester derivative **(64)** was formed from the benzoyl fluoride derivative **(61)**.



(61) **(64)**

Figure 4.18

Ester **(64)** was isolated pure as colourless crystals and the structure was confirmed by X-ray crystallography (Figure 4.19).

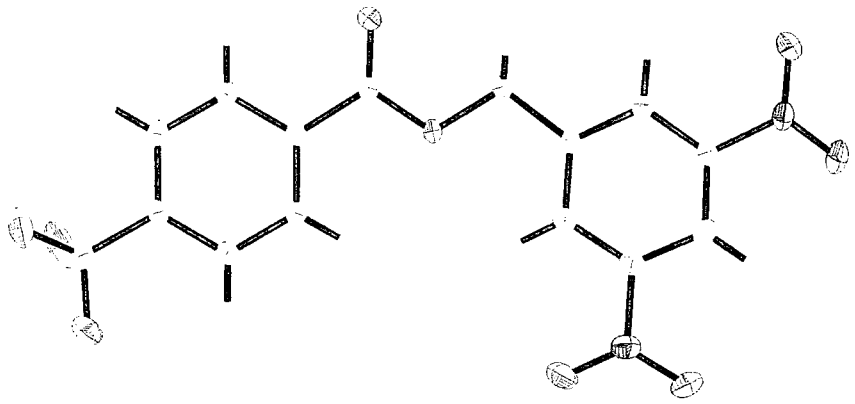
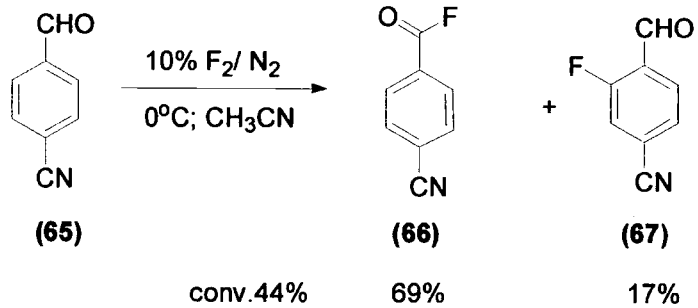


Figure 4.19

In summary, we can conclude that fluorination of the 4-trifluoromethyl benzaldehyde proceeds in a similar manner to the fluorination *meta*-substituted derivatives, with low conversion. Regioselectivity is also low, as fluorination occurs at two sites: at the benzene ring and the carbonyl group.

4.2.7 4-Cyanobenzaldehyde

Direct fluorination of 4-cyanobenzaldehyde **(65)** using 3 equivalents of elemental fluorine resulted in 44% conversion and the formation of three main products, 4-cyano-benzoyl fluoride **(66)** and 6-fluoro-4-cyanobenzaldehyde **(67)** in the ratio 4:1.



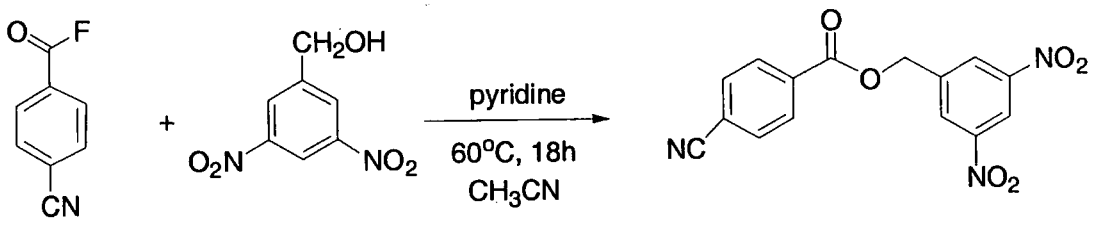
(65) **(66)** **(67)**

conv.44% 69% 17%

Figure 4.21

The product (**67**) was isolated pure and completely characterised. In the ^{1}H NMR spectrum, the presence of only three aromatic resonances in equal ratio indicates that substitution occurred at the ring. Further confirmation of the structure was obtained by ^{13}C NMR, where a signal at 127.5 ppm corresponds to the carbon with adjacent carbonyl group. This signal was found to be a doublet with a coupling constant of 33.7 Hz, which is typical for two bond $^{3}J_{C\text{-}F}$ coupling.

Analogous to the previous examples, 4-cyano-benzoyl fluoride was isolated in the form of an ester (**68**) (Figure 4.21), and spectral data are similar to the spectra of previously described esters, (**55**) and (**64**).



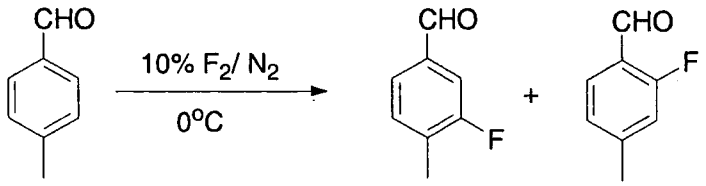
(**66**) (**68**)

Figure 4.21

In summary, we found that direct fluorination of 4-cyano-benzaldehyde (**66**) leads to the formation of two products, (**66**) and (**67**). Although fluorination at the aromatic ring is not selective and occurs at two positions, it is consistent with an electrophilic process since both substituents are *meta*-directing.

4.3.8 4-Toluoaldehyde

Direct fluorination of 4-toluoaldehyde (**69**) using 3 equivalents of fluorine resulted in 58% conversion and gave two main products (Figure 4.22), which were subsequently identified as 3-fluoro-4-toluolaldehyde (**70**) and 2-fluoro-4-toluoaldehyde (**71**) in ratio 7.4:1. A similar result was reported using sulfuric acid as a solvent with a slightly higher conversion but lower selectivity.[123]



(69) (70) (71)

conv.58% 73% 10%

Figure 4.21

After purification, only the main product **(70)** was isolated and confirmation of the structure was obtained using ^{1}H NMR spectrum. The hydrogens from the methyl group were found to be a doublet at 2.23 ppm as a consequence of coupling with fluorine. In the ^{13}C NMR spectrum, carbon of the methyl group was found to be a doublet with a coupling constant of 3.52 Hz, typical of three bonds coupling with fluorine. This indicates substitution at the *ortho*-position to the methyl group.

The second product **(71)** was not isolated due to the low yield (10%), but it was identified according to an authentic sample from Sigma Aldrich.

We found that the methyl substituent increased the selectivity and the conversion of the reaction. Fluorination of the 4-toluoaldehyde is consistent with an electrophilic process giving only one main product, resulting from substitution at the *ortho*-position to the methyl group.

4.2.9 4-Methoxy-benzaldehyde

Direct fluorination of 4-methoxy-benzaldehyde **(72)** using 3 equivalents of elemental fluorine resulted in 66% conversion and gave two main products, 3-fluoro-4-methoxy-benzaldehyde **(73)** and 3,5-difluoro-4-methoxy-benzaldehyde **(74)** in the ratio 1:0.2 (Figure 4.23).

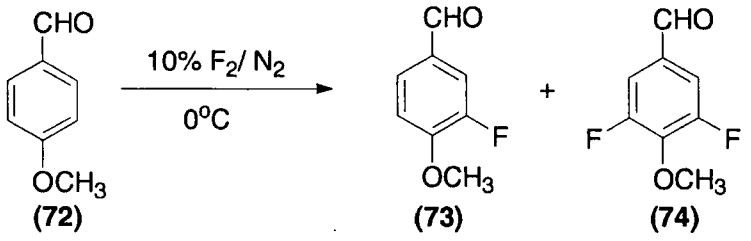


Figure 4.23

Identification of 3-fluoro-4-methoxy-benzaldehyde (**73**) was made by examining ^{1}H NMR data, which showed the presence of a triplet at 3.39 ppm. This triplet corresponds to the methoxy-group and its signal splitting is caused by the vicinity of the fluorine, indicating that fluorine is positioned *ortho* to the methoxy-substituent. Furthermore, in the ^{13}C NMR spectra, C-4 was found to be a doublet with coupling constant 11.1 Hz, which is characteristic of two bond $^{2}J_{HF}$ coupling.

Identification of the second difluorinated product (**74**) was based on the ^{13}C NMR data, where C-3 and C-5 are equivalent due to the symmetry of the molecule. Their corresponding signal was found to be a doublet of doublets with a coupling constant of 252.1 Hz for a one bond carbon-fluorine coupling and 5.96 Hz, which is typical for the three-bond carbon-fluorine coupling. Also, the second order effect was noticed in carbon resonances. The C-4 was found to be triplet due to the vicinity of two fluorines.

Fluorination proceeded exclusively at the ring, likewise with 4-toluoaldehydes. The methoxy-group activates the ring sufficiently, therefore, after initial fluorination, the product reacts further with elemental fluorine to give difluorinated product.

4.3 Summary

The reaction of elemental fluorine with benzaldehydes bearing EWG and EDG was performed to give, in most cases, two products. Their distribution depends on the nature of the substituent and on the solvent employed in the reaction. In all cases, when an EWG is present in the molecule, the reaction occurs preferentially at the carbonyl group, while

reactions of substrates bearing an EDG proceed at the benzene ring exclusively. Benzoyl fluoride was found to be very unstable in the presence of water or other nucleophiles.

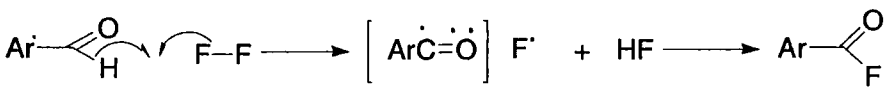
4.4 Discussion of the reaction mechanisms

We found that deactivated benzaldehyde derivatives have two reactive sites, at the carbonyl group and at the benzene ring.

The reaction at the benzene ring probably proceeds via an electrophilic substitution mechanism, since fluorination occurred mainly at the *meta*-position with respect to the aldehyde group. Positions *ortho*- to the carbonyl group are deactivated by resonance and inductive effects, consequently, only the *meta*-position is susceptible to electrophilic attack.

It is not certain whether fluorination at the carbonyl group proceeds via an electrophilic or radical process (Figure 4.24 a and b).

a)



b)

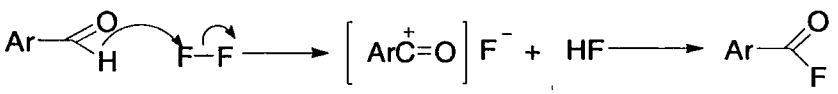


Figure 4.24

In past studies, formation of benzoyl fluorides was also reported in the reaction of benzaldehyde with $CsSO_4F$ (Section 1.9) and it was suggested that the formation of benzoyl fluoride proceeds via a radical mechanism. The ionic mechanism was also suggested, but was excluded after obtaining value for the reaction constant of ρ=–0.38, which is typical of a radical process.

Fluorination of 3-nitro-benzaldehyde was carried out in acetonitrile, formic acid and a mixture of acetonitrile/formic acid. It was demonstrated that the ratio of the products depends on the used solvent (Diagram 4.1).

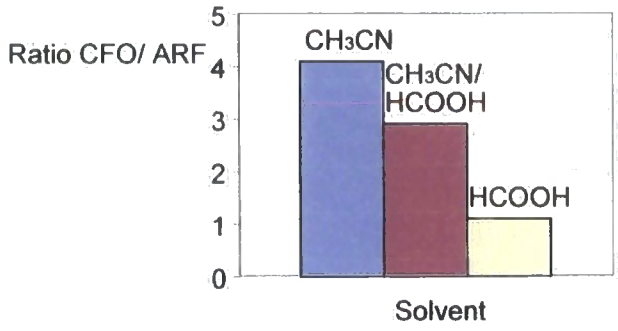


Diagram 4.1 Relative ratios of the products in different solvents

Diagram 4.1 shows that the relative amount of benzoyl fluoride produced is higher in acetonitrile than in the mixture of formic acid/acetonitrile and neat formic acid. It is known that in acidic environments, fluorine is more likely to act as an electrophile. Consequently, the relative amount of the ring-fluorinated product was higher owing to the enhanced electrophilic process. Also, formic acid may protonate the CHO group and deactivate this site for further reaction.

We demonstrated that sulfuric acid is not a suitable medium for the fluorination of deactivated benzaldehyde derivatives, as in the case of other deactivated benzene derivatives (Chapter 3). However, fluorination by elemental fluorine of benzaldehyde derivatives bearing activating substituents in sulfuric acid was reported by Chambers and co-workers.[123] Fluorination take place at the benzene ring exclusively and with good conversion. This implies that the result and efficiency of the reaction does not depend entirely on reaction conditions, but on the choice of the substrate.

We also considered how the variation of substituents, present in the benzaldehyde substrate, affected the distribution of fluorination products in acetonitrile. When nitro- and cyano- substituents were present, benzoyl fluoride was found to be the predominant product, while when other substituents were present (Table 4.6), the relative ratio of products was not as high. We assumed that this variation was caused by a difference in the electron-withdrawing capability of the substituents. Since this total electronic effect of substituents at the benzene ring is described by sigma value (σ-value), we considered the correlation between σ-values and the relative ratio of acylfluoride derivatives and ring-

fluorinated aromatics (Table 4.6, Diagram 4.2). For this analysis, we used ordinary $\sigma_{m(p)}$ values to characterise substituents [137] which are recommended [137] for electrophilic aromatic substitution when electron-withdrawing substituents are present at *meta*-position to the reactive site. Although the reaction on carbonyl group is usually described by $\sigma^{+}_{m(p)}$ but the ordinary $\sigma_{m(p)}$ values can be used also in this case, since their deviations from $\sigma^{+}_{m(p)}$ are very small for most electron-withdrawing substituents.

Table 4.6 Relative ratios of products formed on fluorination of substituted benzadehydes in relation to $\sigma_{m(p)}$-values of the substituents

-X	ArCFO/ArF	$\sigma_{m(p)}$
3-CHO	0.8	0.37
3-CF_3	1.9	0.43
3-CN	3.2	0.56
3-NO_2	4.1	0.71

The second column in the table assigned as ArCFO/ArF, represents the relative ratios of the benzoyl fluoride to the ring fluorinated products and it is presented at the y-axis in Diagram 4.2.

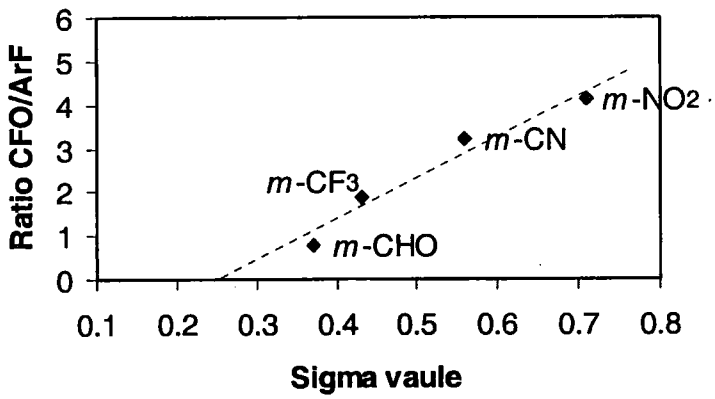


Diagram 4.2 Distribution of the products in dependence of sigma value of the subsistent

Diagram 4.2 shows that the ratio of the products increases almost with σ-value of the substituents. A high σ-value is characteristic of the nitro-substituent and corresponds to its strong electron-withdrawing power. This is because the π-electron density of the ring is

directly conjugated to the substituent with a mesomeric capability. Consequently, the benzene ring is deactivated towards electrophilic attack and the reaction proceeds at the more reactive carbonyl group. Substituents with a lower σ-value are "less electron-withdrawing", thus the benzene ring is less deactivated and electrophilic substitution proceeds more readily at the ring. Finally, when an electron-donating substituent is present, the ring is so activated towards an electrophilic process that the rate of the reaction at the carbonyl group becomes insignificant compared to the rate of aromatic fluorination.

We conclude that two parallel processes operate in reactions of benzaldehyde derivatives with elemental fluorine. Fluorination at the carbonyl group may proceed via the SET mechanism, while reaction at benzene ring proceeds via an electrophilic mechanism.

4.5 Fluorination with Selectfluor™

Although the reaction of some 1,4-substituted deactivated derivatives with Selectfluor™ have been reported,[68] we decided to perform fluorinations with *meta*-substituted benzaldehyde derivatives to compare with the our results from fluorination using elemental fluorine (Section 4.2).

Fluorination of the selected benzaldehyde derivatives, (Table 4.7) bearing electron-withdrawing substituents, was performed with Selectfluor™ at reflux temperature (Figure 4.25). The reaction proceeds only benzoyl fluoride, as shown by ^{19}F NMR spectrum. The peak was found to be a singlet with chemical shifts usually between 19-21 ppm. Analogous to the reaction with elemental fluorine, benzoyl fluorides were isolated after esterification.

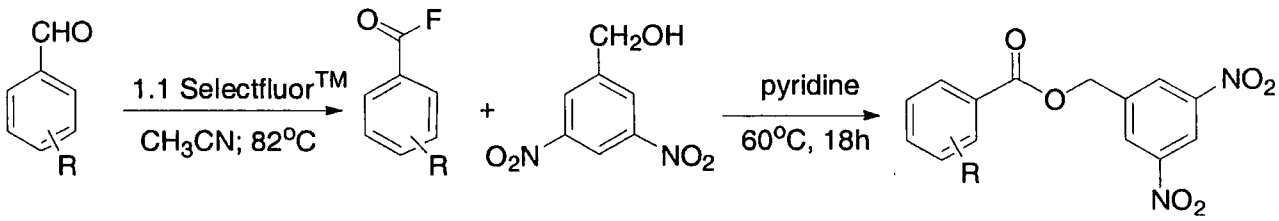


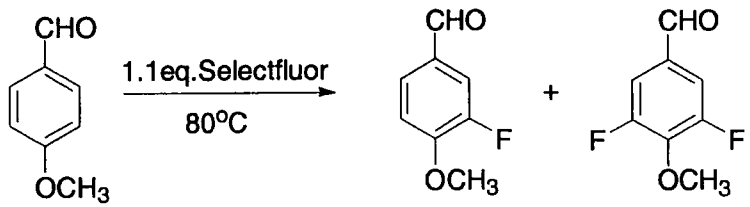
Figure 4.25

Table 4.7 Fluorination of benzaldehydes using Selectfluor™

Entry	Substrate	Conversion %
1	3-nitrobenzaldehyde	69
2	3-formylbenzonitrile	78
3	Isophthalobenzaldehyde	84
4	4-Trifluormethyltolualdehyde	87

The reaction resulted in very high conversions for the most of the examined substrates (Table 4.7). The lowest conversion was obtained in the case of isophthalaldehyde (entry 3) regardless of two carbonyl groups are present. It is also worth noting that fluorination at the ring did not occur, even in small amounts, for any attempted substrate.

We decided to examine fluorination of benzaldehydes with electron-donating group using Selectfluor™. 4-Methoxy-benzaldehyde **(72)** was reacted with Selectfluor™ to give two main products, 3-flouro-4-methoxy-benzaldehyde **(73)** and 3,5-difluoro-4-methoxy-benzaldehyde **(74),** with ratio 6.1:1 in 51% conversion.



(72) **(73)** **(74)**

51% 6.1 : 1

Figure 4.26

Both products were identified by comparison with the previously isolated products from the reaction with elemental fluorine. Selectfluor™ appears to be slightly less reactive than elemental fluorine in reaction with 4-methoxy-benzaldehyde (**72**), but distribution of the products is very similar. In this reaction, as in the one with elemental fluorine, no benzoyl fluoride was produced. Our conclusion is that substituents, such as methoxy and methyl donate electrons into the ring and thus make the ring a reactive site for electrophilic fluorination.

4.6 Discussion of the reaction mechanism

In comparison to the reactions using elemental fluorine, reactions where Selectfluor™ was used as a reagent instead, are more selective. When electron-releasing substituents are present, the reactions occur selectively at the carbonyl group. It is not clear via which mechanism this reaction proceeds. Banks[123] has suggested that oxidation of the benzylic alcohols with Selectfluor™ proceeds via a SET process and a similar process can be expected aldehydes are involved.

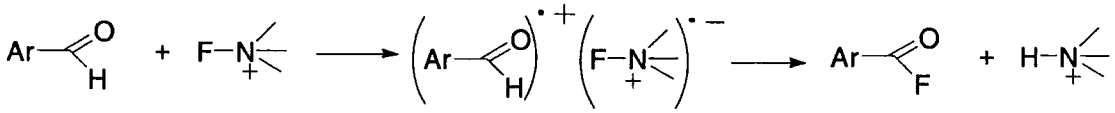


Figure 4.27

The reaction may proceed via a charge transfer complex which leads to the formation of the benzoyl fluoride (Figure 4.27).

Electrophilic attack is also possible, forming a very stable intermediate (Figure 4.28).

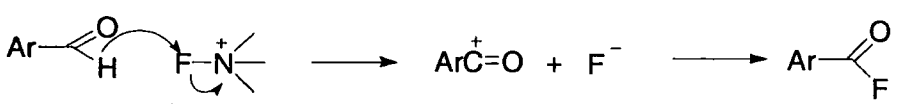


Figure 4.28

When the substrate possesses an electron-donating substituent, for example 4-methoxy-benzaldehyde, the reaction is consistent with an electrophilic process.

4.7 Conclusions

We conclude that fluorination of benzaldehyde and its deactivated derivatives proceeds at two sites and in significantly higher conversion than the other disubstituted deactivated benzene derivatives.

Two main products were formed: benzoyl fluoride and a ring-fluorinated aromatic product. Correlation between the ratio of these two products and sigma-value was established.

It was concluded that stronger electron-withdrawing group in benzaledehyde deactivates the ring towards fluorination and promotes side-chain reactions. In this way, the use of elemental fluorine cannot always be a suitable replacement to widely used Halex and diazotization methods for the production of fluoro-benzaldehydes.

When electron-donating substituents are present, the reaction is selective and proceeds at the benzene ring consistent with an electrophilic process. With this class of compounds, use of elemental fluorine and Selectfluor™ can be considered as an efficient and simple route to fluorinated benzaldehydes.

Selectfluor™ was shown to be a more regioselective reagent, providing the product in high conversion in all cases. When an electron-withdrawing substituent is directly bonded to the benzene ring, the reaction proceeds exclusively at the carbonyl group, whereas electron-donating substituents activate the benzene ring towards fluorination.

Chapter 5 Fluorination using microreactor (MR) technology

5.1. Introduction

Use of elemental fluorine gives rise to several problems regarding safety, due to its corrosive properties and often vigorous reactivity, and concerning demand for large heat transfer, because the reaction with organic substrates are often exothermic. Furthermore, poor mixing in batch condition does not enhance the solubility of fluorine gas in desired solvents and results often insufficient contact between fluorine and substrate. The following section describes the advantages of using microreactor technology for fluorination and how existing problems connected with use of elemental fluorine can be overcome.

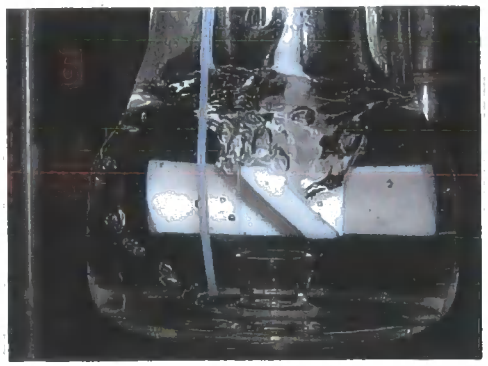
The previous two chapters described fluorination of deactivated benzene derivatives using elemental fluorine, which is characterised by good selectivity of monofluorinated products and relatively low conversions. Since microreactor devices can be used for the intensification of processes, we decided to perform fluorination of the previously studied substrates, benzaldehyde derivatives and nitrobenzene derivatives, using microreactor techniques. These results and their discussion are presented in this chapter.

5.2. Microreactors: definition and advantages

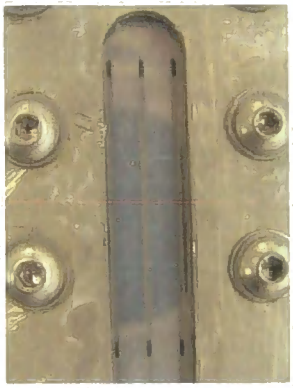
There are several definitions which describe microreactors from different viewpoints. Microreactors are miniature housings for carrying out chemical reactions in channels that have a diameter between 100-1000 microns and channel length of several centimetres.[138] From the aspect of design and fabrication of reactors, microreactors are defined as miniaturised reaction systems fabricated by microtechnology and precision engineering.[139] From the aspect of chemical synthesis, they are defined as a series of channels formed in a planar surface in which small quantities of the reagent can be manipulated.

Microreactors should not be considered just as smaller versions of standard macroreactors. Reduction in size brings to process new qualities and often radically different reaction conditions from those in more traditional devices. Therefore, major benefits for the process of fluorination with elemental fluorine are the following:

- **Increased surface-to-volume ratio**. Improved surface-volume ratio ensures better heat and mass transfer.[138] The heat transfer coefficient is improved by an order of magnitude, so this allows better temperature control and reduces the appearance of the 'hot spots'. This is very important for fluorination using elemental fluorine. Reactions are usually conducted at low temperatures (usually in the range -30°C to 10°C), since radical processes can interfere at higher temperatures.[140] Elemental fluorine reacts exothermically with organic compounds (Section 1.6.1.4) so elimination of 'hot spots' and better control of temperature reduces undesired side reactions. Further benefits of the increased surface-to-volume ratio for reaction using fluorine gas are expected due to the improved specific interface area of gaseous and liquid phase. The reactants are also in better contact due to better diffusion of fluorine through a thin layer of liquid phase. For catalysed reactions, increased surface volume ratio enhances efficiency significantly.[141]
- **Safety**. Use of small quantities of reagents, in a particular moment, reduces possible exposure to hazardous and toxic material. In addition, it has been demonstrated that reactions can be operated safely under conditions which could otherwise, in standard batch reactors, lead to explosive processes.[142] For example, using gas mixtures with about 50% of fluorine content and solutions of organic molecules is regarded as a dangerous process, but no studies using microreactor devices for direct fluorination reported, explosions, so far.[143] Also, a small reaction volume in combination with good heat adsorptions provides excellent safety.
- **Very efficient mixing**. In microreactors, efficient mixing prevents a concentration gradient. When elemental fluorine is used as reagent for fluorination, good mixing is very important to enhance contact between the fluorine gas and solution and to afford their uniformed distributions. Often, it is very difficult to achieve good mixing in batch reactor (Figure 5.1, a).



a) poor mixing



b) large surface area provides better mixing of gas and liquid in microchannels

Figure 5.1

Use of microreactor channels for gas liquid reaction allows better contact and availability of fluorine to react with the substrate (Figure 5.1, b).

- **'Scale out' instead of 'scale-up'.** Microreactor technologies have great potential for application in industrial production but cannot be used for classical process development by an increase of reactor size. 'Scaling-out' (replication of microreactors units) instead of 'scaling up' would eliminate the costly process of going from lab to pilot plant and full scale production, intensify the process and reduce the size of the chemical plant.[42, 144-146] Also, in this way, failed units can be easily replaced without interfering with other equipment and units.

There is significant interest in the use elemental fluorine as a reagent, due to the much lower price in comparison to other fluorinating agents. Use of microreactor devices offer the possibility to overcome the disadvantages involved in the use of this gas (hazardous properties and difficult control of the reaction).

5.1.2 Literature overview

Microreactors and their application in recent years have undergone spectacular development in versatile areas of organic chemistry.[147-149] A large number of publications

for synthesis of fluorinated compounds using microreactors have been reported.[150] Consequently, we limited this literature overview on recent publications involving the use of elemental fluorine as the most relevant to the present work.

A one channel microreactor (Figure 5.2) was designed for selective fluorination and perfluorination using elemental fluorine as a reagent by Chambers and co-workers.[138] The base of this horizontal type of reactor was made from nickel block which contains the channel (500 μm width and depth). The top of the channel is sealed by a PTFE window to enable visualisation of the reaction. The solution with substrate is introduced into the reaction channel through inlet into one end of the reactor and was controlled by syringe pump drive. Fluorine inlet is placed 30 mm from substrate inlet along reaction channel and its flow was controlled by mass-flow controller.

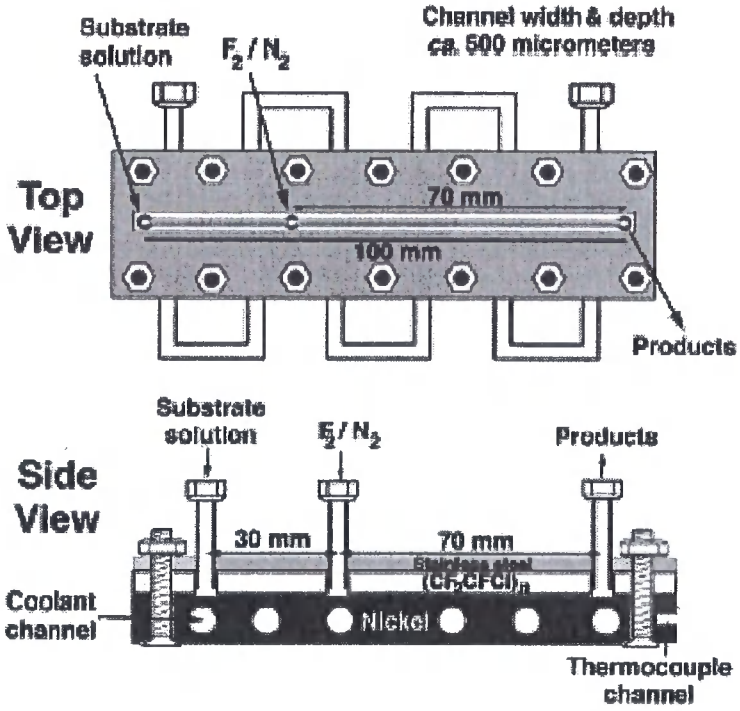
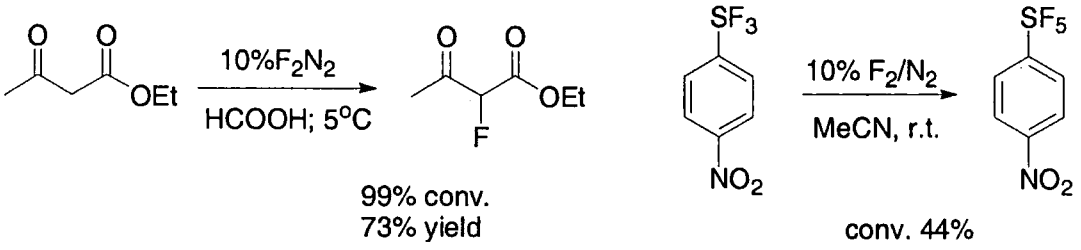


Figure 5.2

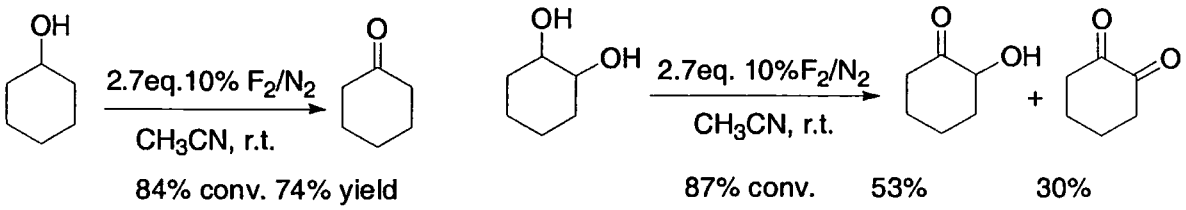
Successful fluorination of dicarbonyl derivatives (a) and trifluorosulfides (b) demonstrates the versatility of this methodology in microreactor (Figure 5.3). Significant improvement in conversion of β-keto ester into fluorinated analogue was achieved compared to the bulk fluorination proving efficiency of this system.



(a) (b)

Figure 5.3

It was concluded that the reactions proceeded more efficiently due to the improved contact between phases and due to the catalytic effect of the metal surface of the microreactor. Later, successful oxidation of various alcohols was reported using the same microreactor (Figure 5.4).[151]



(a) (b)

Figure 5.4

Oxidation of the cyclohexanol was studied in the batch conditions[152] and resulted in lower conversion and selectivity than one in the microreactor. Furthermore, oxidation of the both hydroxyl groups was achieved using microreactor (Figure 5.4 b) while in the batch conditions only α-hydroxy ketone was obtained using similar amount of elemental fluorine.

Chambers and co-workers demonstrated that scaling-out of this microreactor was possible by replication of the channels (Figure 5.5).[146] The multi-channel reactor consisted of three channels with separate inlets for the substrate and fluorine gas and three outlets for the reaction mixture.

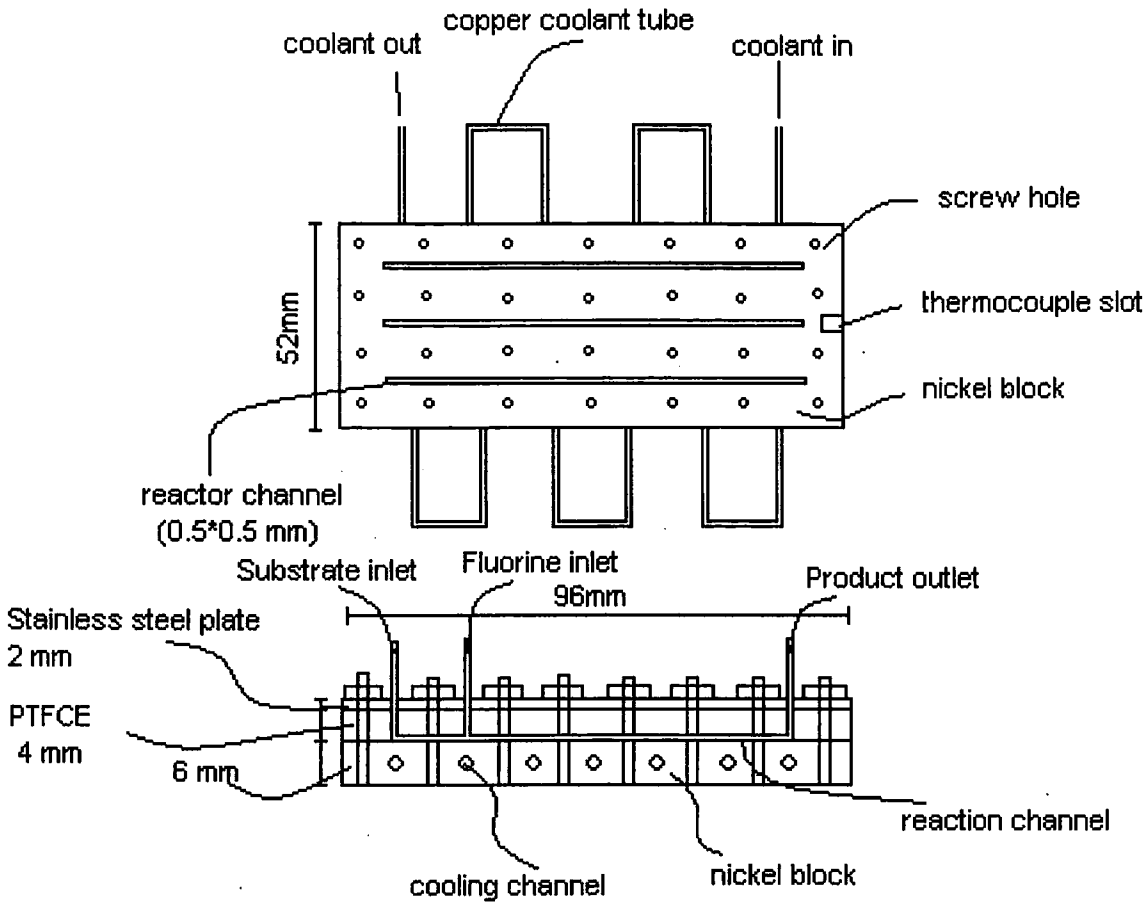


Figure 5.5

The highest conversion for the fluorination of 4-nitrotoluene was achieved using acetonitrile and formic acid (3/2 ratio) as solvent and resulted in 77% conversion with reasonable selectivity.

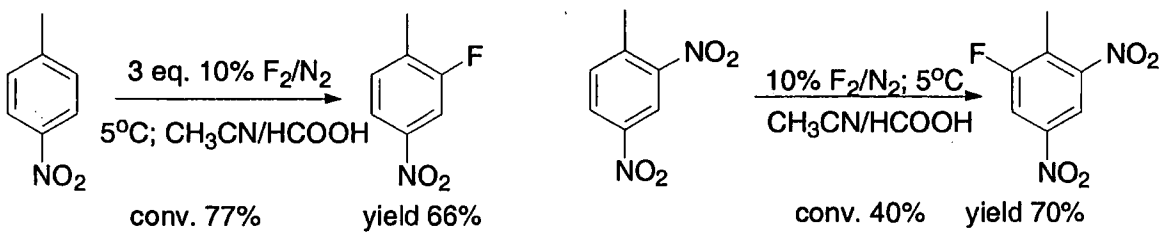


Figure 5.6

Relatively good conversion of 2,4-dinitro-toluene was also achieved using this type of reactor.

Jähnisch[143] and co-workers reported a detailed comparative study of the efficiency of three types of reactor: the falling film microreactor (FFMR), micro bubble column (MBC) (both made of stainless steel) and laboratory bubble column (LBC), as shown in Figure 5.7.

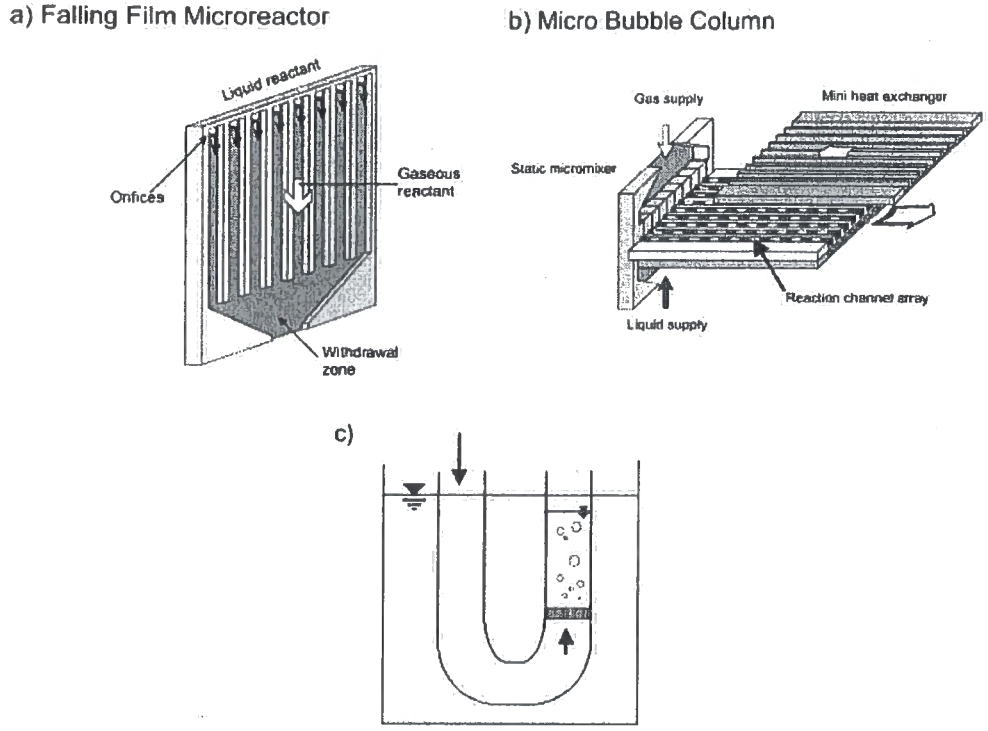


Figure 5.7

FFMR consists of the vertical platelet comprising large number of channels which can generate films down to 25 μm thickness. MBC contains mixing unit and horizontal channels. Depending on the velocity of the gas phase, flow pattern was found to be bubbly, slug and annular.

Fluorination of toluene was performed in all three reactors and resulted in the formation of monofluorinated products (Figure 5.8), but di- and trifluorinated products were also found.

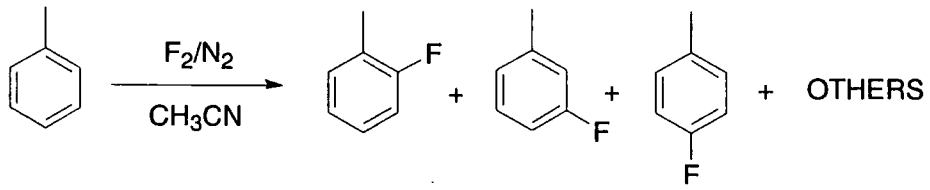


Figure 5.8

It was considered how varying the fluorine-toluene ratio, temperature, concentration and residential time influence the reaction. Efficiency of the reactors was estimated according to conversion as function of the molar ratio of fluorine to toluene (Diagram 5.1).

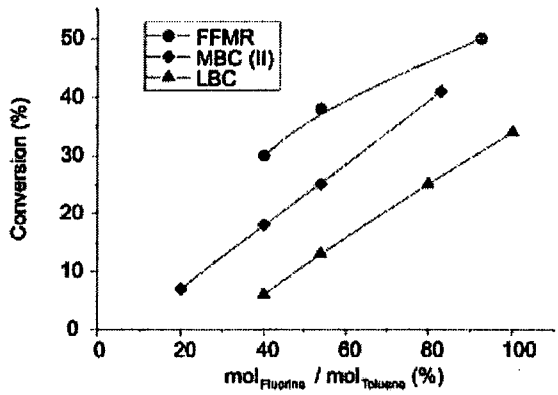


Diagram 5.1

In diagram 5.1, we can see that highest conversions were achieved using the FFMR while the lowest conversions were achieved for the LBC. The efficiency of the two microreactors exceeded those of LBC, probably due to huge difference in interfacial areas which were estimated to be 27000 m^2/m^3 for FFMR, 9800 m^2/m^3 for MBC and 50-600 m^2/m^3 for LBC. Increase of the residential time does not have an impact on the conversion of the reaction which was explained by the presumption that diffusion is not a limiting factor.

Inspired by the concept of microreactors made at Durham[145, 153] and Hull,[144, 149] Syngenta has also designed a microreactor for fluorination using elemental fluorine[154]. They used PTFE channel gaskets placed in a base, connected with a top plate by the hinge. The reactor is suitable for fluorination using a range of solvents (acetonitrile, methanol, HCOOH, conc. H_2SO_4) and temperatures (from -30 to +40). Using this reactor system, fluorination of monosubstituted benzene derivatives and β-diketones was achieved and results are comparable to fluorination achieved by other designs.[139, 145] Regioselectivity was

very similar to the one obtained in the batch conditions, while conversion was enhanced significantly (94%).

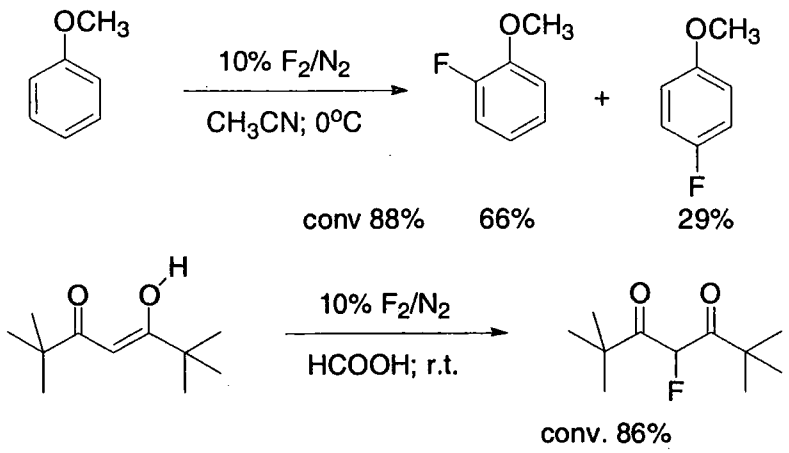


Figure 5.9

5.2 9-Channel microreactor design

Microreactor designed by Chambers and co-workers[145] was used in this work, so the device and its operation are described in detail here (Figure 5.10).

A fluorine inlet is placed at the top of the device (Figure 5.10) where the pressure driven gas enters into the reservoir at the top of the stainless steel base block (Figure 5.11). The substrate reservoir is placed directly under the gas reservoir. Both reservoirs are directly connected to the reaction channels. At the bottom of the microreactor channels, a third reservoir is used to collect the products. Substrate flow is regulated by a syringe pump drive. After passing through the microreactor device, organic products are easily separated from the stream of gases by cooling the liquid receiver with ice. Unreacted fluorine gas is directed to the soda-lime scrubber.

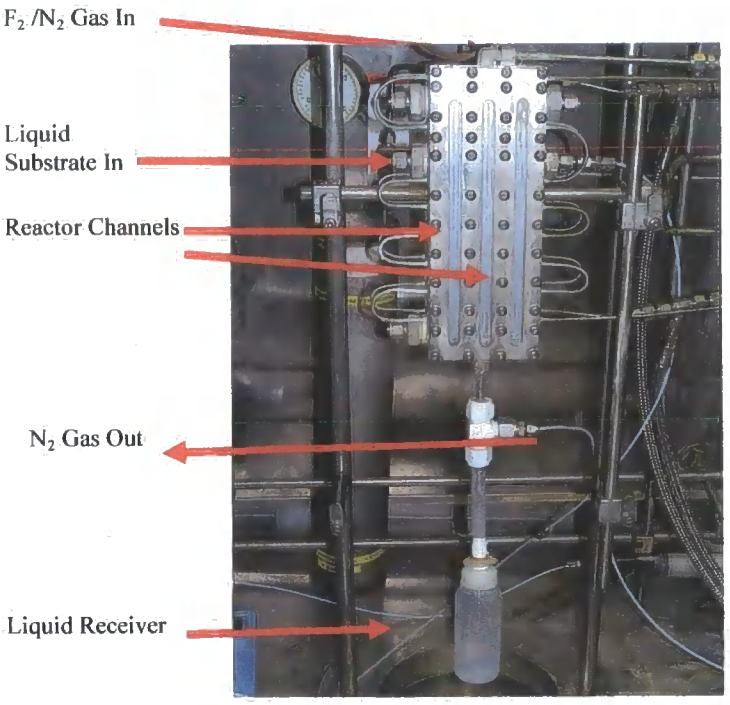
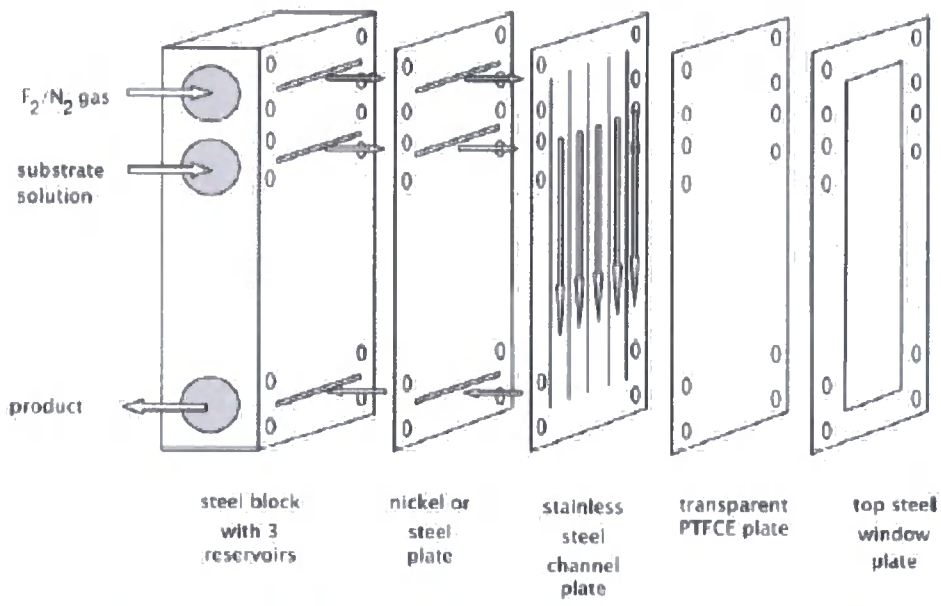


Figure 5.10

The microreactor itself consists of several layers (Figure 5.11) attached to the stainless steel base. The first layer, next to the stainless steel base, is nickel or steel plate. The channel plate is placed as the second plate in order from base block and is produced from stainless steel sheets using standard discharge techniques. The volume of the channels, where reaction proceeds, is determined by thickness of the plate (0.5 mm) and width of the slots (0.5 mm) in the plates. The length of the channels is 20.2 cm. The final layers PCTFE and stainless steel frame allow visualisation of the reaction. All plates are compressed together by screw fittings and sprayed with PTFE to prevent eventual leakage.



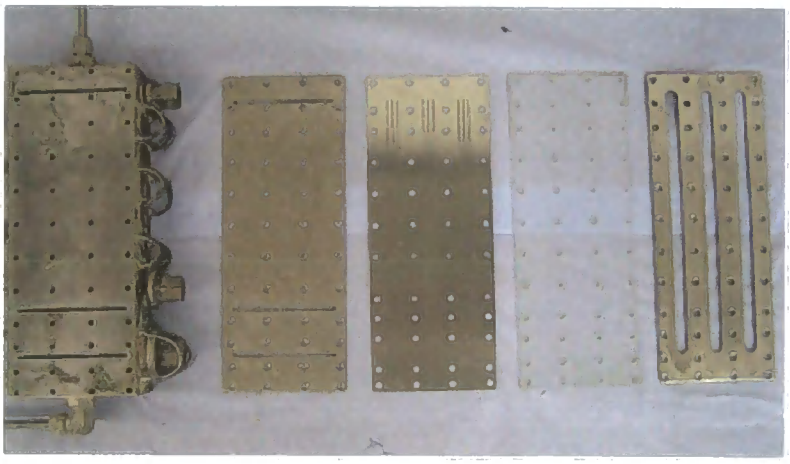


Figure 5.11

All plates are manufactured very easily in our workshops and their maintenance and replacement of corroded plates is very easy and inexpensive. Furthermore, variation of plates with different number of channels (3, 9, 18 and 30 channels) allows scale-out (Figure 5.12).

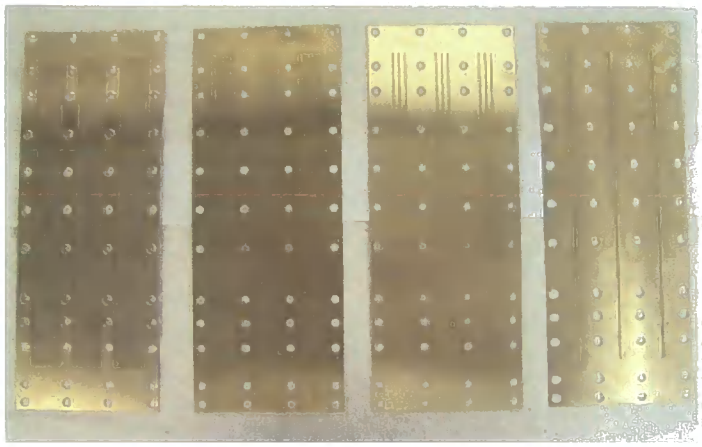


Figure 5.12

A detailed description of the manipulation of the microreactor is presented in Section 6.2 of the experimental chapter.

During fluorination, fluorine gas flow rate was kept above 60 ml min^{-1} to obtain annular flow (Figure 5.13, a), where the liquid coats the channel walls, while gas is mainly flowing through the center of the channel. This kind of flow provides the best mixing between solution and fluorine.

(a) (b)

Figure 5.13

Slug flow (Figure 5.13, b) is characterised by the presence of sections of liquid ("slugs") which are now "trapped" between traveling bubbles of the gas. In the channels, this flow is observed with lower fluorine flow rate and is undesirable, since lower conversions were observed.

Successful fluorination of dicarbonyl compounds using this microreactor has been achieved using 3-, 9-, 18- and 30- channels plates (Figure 5.14).

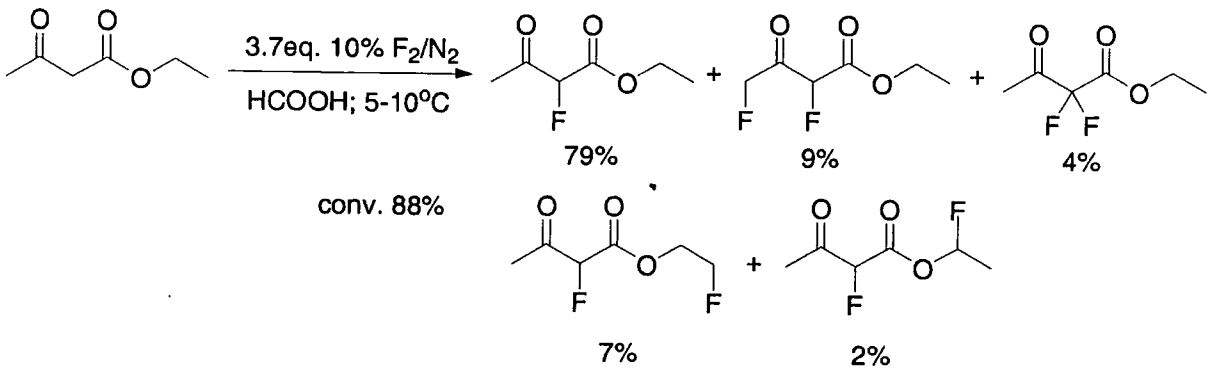


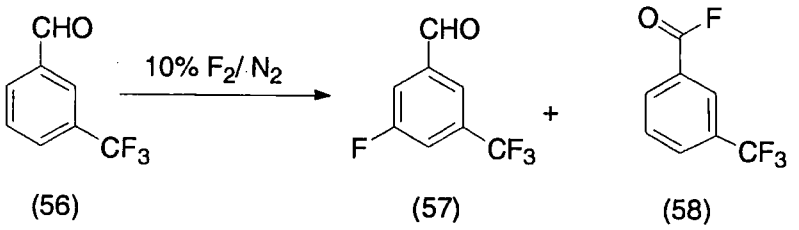
Figure 5.14

5.3 Fluorination of deactivated benzene derivatives

We found that direct fluorination of deactivated benzaldehyde derivatives in a standard batch glass reactor (Chapter 4) gave relatively low conversions (22-44%). We performed fluorination of these compounds in microreactor to compare with batch conditions in the hope of achieving higher conversions.

5.3.1 Benzaldehydes

Direct fluorination was initially performed using 3-trifluoromethyl-benzaldehyde because its good solubility in acetonitrile and possibility of the simple monitoring of the reaction by ^{19}F NMR spectroscopy due to the presence of fluorine in the starting material and products. Based on the optimisation of conditions in our previous work,[145] the flow rate of the substrate was set to be 4 ml $h^{-1}ch^{-1}$ (Table 5.1, entry 1). In this reaction 3 equivalent of the fluorine were used and resulted in a lower conversion compared to the batch conditions. Only 12% of the starting material was converted to the products. However, products **(57)** and **(58)** were obtained from MR as found under batch conditions.



(56) (57) (58)

Figure 5.15

Table 5.1 Fluorination of 3-trifluoromethyl-benzaldehyde

Entry	Fluorine: Substrate ratio	Substrate flow ml $h^{-1}ch^{-1}$	Conv. (%)	Yield **(57)** (%)	Yield **(58)** (%)
1	3	4	12	29	64
2	3	2	57	31	59

The duration of the reaction was only 66 min. Consequently, we believe that the residential time was too short for the reaction to proceed in a reasonable conversion. It is worth noting that the similar distribution of the products was obtained under batch and microreactor conditions.

We performed fluorination using a slower substrate flow (Table 5.1, entry 2) which resulted in a longer residential time of the substrate and fluorine in the microreactor channels. Consequently, conversion was increased 4.75 times. It is important to note that the concentration of the substrate in solution was increased and the ratio of the elemental fluorine to substrate was kept as 3: 1. We presume that residential time is a crucial factor since no effect of concentration on the conversion was noticed in the batch reactor.

Fluorination of other benzaldehyde derivatives (Table 5.2) resulted in significant increases in conversions and in all cases the two expected products were formed.

Table 5.2 Fluorination of benzaldehyde derivatives in microreactor

Substrate	Conv. (%)	Yield I (%)	Yield II (%)
3-nitro-benzaldehyde	52	16	76
3-formyl-benzonitrile	48	22	74
isophthalodialdehyde	46	23	65

I: 5-fluoro-benzaldehyde derivatives; II benzoyl fluoride derivatives; in all entries: substrate flow was 2 ml min^{-1} ch^{-1}

The relative ratios of the products remained similar to the batch reaction, so we conclude that the kinetic characteristics of the reaction have not been altered.

In conclusion, we demonstrated that fluorination of benzaldehydes can be increased significantly by using a microreactor. Improved contact between fluorine and substrate plays an important role in intensification of the process. Therefore, for further development of the application of microreactor, we chose substrates that have higher selectivity in the reaction with elemental fluorine: cyano- and nitrobenzene derivatives.

5.3.2 Nitrobenzene derivatives

Fluorination of 3-nitro-benzonitrile **(33)** was performed using a batch reactor and proceeded with very low conversion (8%) (Section 3.2). When this reaction was performed in MR, it resulted in 18% conversion producing only one main product, 5-fluoro-3-nitro-benzonitrile.

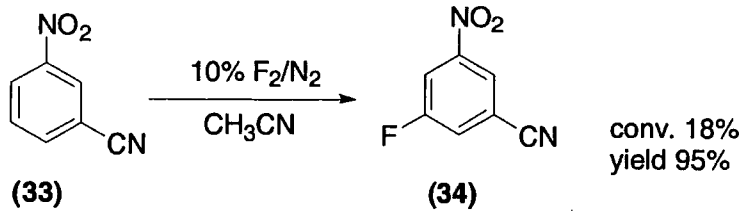
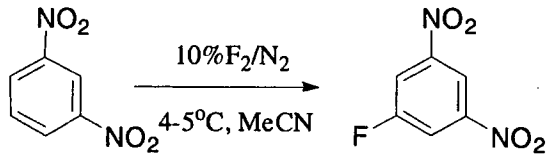


Figure 5.16

It is important to note that 3 eq. of elemental fluorine were used in both batch and microreactor conditions. Substrate flow was 0.5ml $h^{-1}ch^{-1}$.

1,3-Dinitro-benzene was also fluorinated in the microreactor using substrate flow rates of 0.5 ml h^{-1} min^{-1} and 0.1 ml h^{-1} min^{-1} and the maximum conversion was achieved with the slower flow rate (Table 5.3, entry 2). The conversion was three times higher than the one achieved in a batch reactor (Section 3.2).



(31) (32)

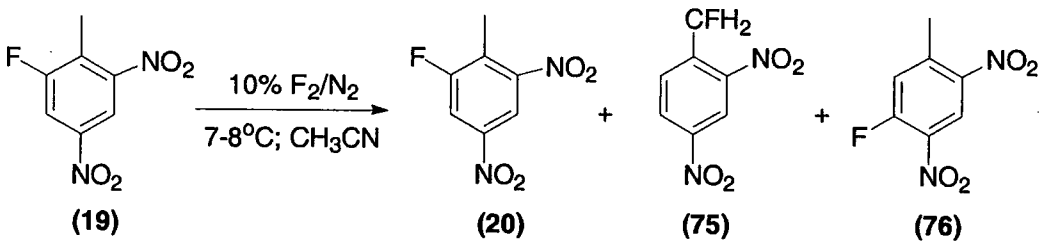
Figure 5.16

Table 5.3 Fluorination of 1,3-dinitro-benzene

Entry	Fluorine: substrate ratio	Substrate (ml $h^{-1}ch^{-1}$)	Conv. (%)	Yield (%)
1	3	0.5	18	95
2	12	0.1	27	95

Further decrease of the flow rate of the substrate was attempted, but gave rise to the problem of the solidification of substrate in the channel causing disruption of flow of the both gas and liquid phase.

2,4-Dinitro-toluene contains one mildly activating methyl group but has very low reactivity towards fluorination. When a substrate flow of 2 ml h^{-1} ch^{-1} and 3eq. elemental fluorine were used, the reaction resulted in 38% conversion giving only one main product **(20)** (Table 5.4, entry 1), similar to the result reported a using three channels MR (Section 5.12, Figure 5.5).[146]



(19) **(20)** **(75)** **(76)**

Figure 5.18

Table 5.4 Fluorination of 2,4-dinitro-toluene in microreactor

entry	subs. flow (ml $h^{-1}ch^{-1}$)	conv. (%)	yield **(20)** (%)	yield **(76)** (%)	yield **(77)** (%)
1	2	38	98	>1	-
2	0.1	98	53	23	18

Performing the reaction with a substrate flow of 0.1 ml $h^{-1}ch^{-1}$ and 12 eq. of fluorine, a complete conversion of the starting material **(19)** was achieved. However, regioselectivity was significantly decreased. The reaction gave three main products which were subsequently identified as 6-fluoro-2,4-nitro-toluene **(20)** in 53% yield, 2,4-dinitro-fluoromethyl-benzene **(75)** 23% and 5-fluro-2,4-nitro-toluene **(76)** 18%.

Structure of compound **(76)** was confirmed by comparison with literature.[155] In the ^{19}F NMR spectrum, fluorine at the methyl group was found to be a triplet coupled by adjacent hydrogens with coupling constant of 45.8 Hz, which is typical for two bonds coupling of saturated compounds. Compound **(76)** was identified by ^{1}H NMR, where it was found to have only two aromatic proton signals. Coupling constant for the remote H-3 proton was 2.8 Hz, which is in agreement with $^{3}J_{HF}$ three bonds coupling constant.

An increase of the relative amount of fluorine (from 3 to 9 eq.) in batch conditions did not result in an enhancement of the conversion. Fluorine consumption in the microreactor is more efficient due to the better contact between the liquid and gas phase. This is probably the main reason that the reaction resulted in high conversion. Since the reaction is not very selective, it is possible that the products were obtained by radical mechanism (Section 1.6.1.4, Figure 1.8).

We can conclude that higher conversions were achieved using microreactors, as the reaction vessels. Regioselectivity was mainly preserved, with an exception of 2,4-dinitrotoluene, where additional products were obtained.

5.4 Conclusions

We found that fluorination of deactivated benzene derivatives using elemental fluorine in the 9 channel microreactor resulted in significant improvement in conversion, comparing to the standard batch conditions.

Dependence of the conversion with respect to the flow of substrate is established. A decrease in the substrate flow rate provides higher conversion, but sometimes can result in less selectivity. Furthermore, the variation of the amount of fluorine used in the reaction has more pronounced effect on the conversion when reactions were performed in the microreactor in comparison with those carried out in the batch conditions.

Fluorination of *deactivated benzaldehyde* derivatives proceeds with a moderate conversion and the distribution of the products is similar to that obtained in a batch reactor.

Nitrobenzene derivatives react with elemental fluorine regioselectively but high conversions can not be achieved due to strong deactivation of the ring. The presence of methyl substituent improves reactivity significantly, so complete conversion was achieved using microreactor technology.

Chapter 6 Experimental to Chapter 2

6.1 Instrumentation

Reagents:

The reagents were supplied from Aldrich, Avocado, Lancaster and Fisher.

Gas liquid chromatography:

Gas chromatography was performed on a Hewlett Packard 5890 Series II gas liquid chromatograph equipped with a 25 m cross-lined methyl silicone or 5% phenyl methyl silicone capillary column with a flame ionization detector. The temperature of the column is 40°C, rising to 300 °C by 10 °C/min. The temperature of the injector is 250 °C and of the detector is 300 °C.

Elemental Analysis:

Elemental analyses were carried out on an Exeter Analytical CE-440 elemental analysis machine.

NMR Spectorscopy:

NMR spectra were recorded in chloroform-D, acetone-D, acetonitile-D and dimethylsulfoxide-D from following spectrometers: Varian Gemini 200, Varian Mercury 200, Varian VXR 400S or a Unity Inova 500 NMR spectrometer. Internal references were trichlorofluoromethane, tetramethylsilane and chloroform. The coupling constants are reported in Hz, chemical shifts in ppm units.

IR Spectra:

Infrared spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer using thin films between KBr-disks or KBr-plates.

Mass Spectroscopy:

Mass spectra were recorded on a Thermo Finnigan Trace MS mass spectrometer (for EI^+), Fisons VG Trio 1000 mass spectrometer coupled Hewlett Packard 5890 series II gas chromatogaph (for CI^+) or Micromass LTC (for ES^+). Accurate mass spectra are recorded by Micromass Autospec Mass Spectrometer and the EPSRC national mass spectroscopy centre.

Melting points:

Melting points are measured at a Gallenkamp melting point apparatus and are not corrected.

6.2 Apparatus for the use of elemental fluorine

Elemental fluorine is commercially available in high pressure gas cylinders as 20% and 50% F_2/N_2 mixtures. Since fluorine is a very reactive and toxic gas, the apparatus is specially designed to allow the performance of safe and controllable reactions.

The manifold systems were constructed using 1/4" stainless steel tubing, Monel® or stainless steel Swagelok® valves, stainless steel fittings and was placed into vented stainless steel fumes cupboards. After its construction or replacement of any part of the manifold, pasivation (passing conc. F_2/N_2 mixture) is necessary before its use for any reactions.

For experiments presented in this thesis, the apparatus presented in the Figure 6.1 was used. It contains reservoir (secondary cylinder), which are supplied with fluorine from the main cylinder. The reaction was supplied with fluorine exclusively from this secondary cylinder, which are usually diluted until 20% or 10% fluorine/nitrogen mixture. Nitrogen is supplied from a high-pressure cylinder (Size K) at a pressure of approximately 230 bar.

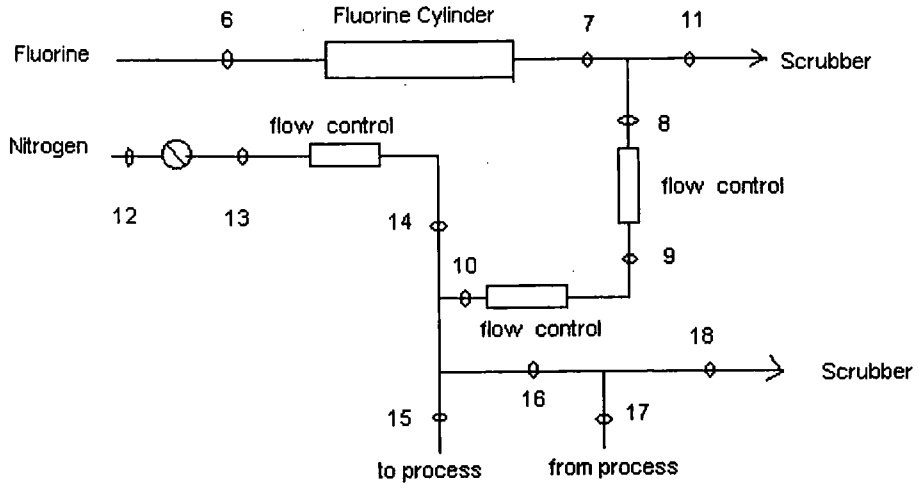


Figure 6.1

In the secondary cylinder (Figure 6.1) it is possible to fill up to a maximum pressure of 5 bar. Fluorinations are always performed using the same procedure.

Operation of Right hand Rig Fluorination Procedure (Figure 6.1)

1) Ensure all valves are closed.
2) Reaction vessel (Figure 6.1) is attached to the "to process and from process" connections and cooled to 0°C using a cryostat.
3) Open valves 15, 17 and 18.
4) Open valves 12 and than slowly open 13 to regulate the flow rate of the nitrogen.
5) The reaction vessel should than be purged by nitrogen for a minimum of 20 min (flow 50 ml/min).
6) Close valve 12 and 13 or regulate the flow of the nitrogen if further dilution of F_2/N_2 mixture is necessary.
7) Open valves 7, 8 and 10.
8) Slowly open valve 9 (fluorine flow is automatically regulated using flow controller Brooks 5850S)
9) Termination of the experiment involves closing valves 7 and 8
10) When the flow of fluorine is zero, close valves 9 and 10

11) Nitrogen control valves (12 13 and 14) should be open for 20 min to purge the system with nitrogen (50 ml/min) to eliminate any remaining fluorine.

12) Close valves 12, 13, 14, 15, 17 and 18.

The reaction vessel is made of glass (Figure 6.3.) and is connected with fluorine/ nitrogen manifold with PTFE dip-pipe and any exit gases were piped from the reactor to a scrubber, filled with soda lime.

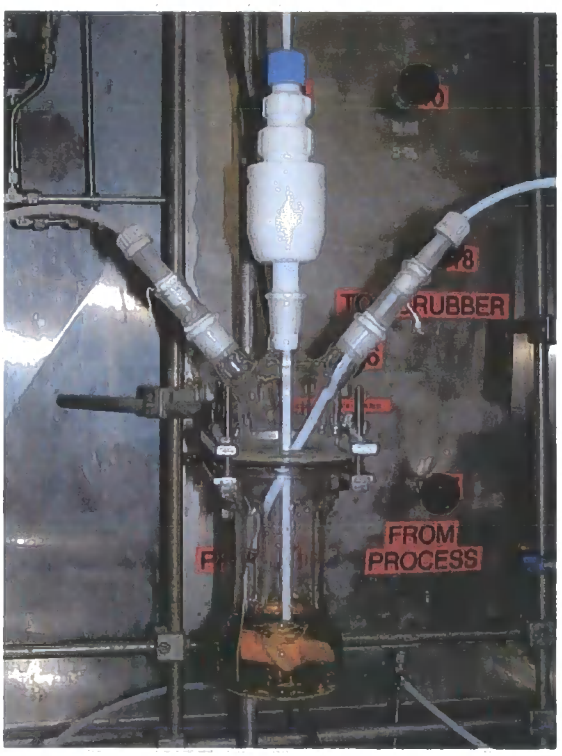


Figure 6.3.

Mixing is provided by a stirrer powered by an IKAMAG motor (max. 2000rpm) which is fitted into a glass stirrer guide and placed in the center of the base of the reactor.

Alternatively, "to process and from process" can be attached to the microreactor which is also situated in the fume cupboard.

6.3 General procedure

Elemental fluorine

The reactions were performed by the following procedure unless otherwise stated. A solution of the substrate was placed in the glass reactor fitted with an overhead stirrer. A cryostat was set at −8.5°C to cool the solution to 0°C and nitrogen was passed through for 30 min.

The reaction was performed by passing 10% fluorine gas, diluted in nitrogen, through the mixture at a flow rate of 50 ml min^{-1}. After completion of the reaction, nitrogen was purged through the reaction mixture for 15 minutes.

The reaction mixture was poured into water (150 ml) or in some experiments, neutralized with $NaHCO_3$, extracted with 3 portions of dichloromethane (100 ml) and then dried with $MgSO_4$. After filtration, solvent was evaporated at reduced pressure using a rotatory evaporator. In the case of high boiling point compounds, crude product was additionally dried at higher vacuum on a vacuum line. Conversion and yields were estimated by ^{19}F NMR by adding a measured amount of reference compound fluorobenzene to the crude material to compare ratio of the integrals or by ^{1}H NMR.

Purification was achieved using column chromatography, Kugelrohr distillation or recrystalisation.

Selectfluor™

A solution of the substrate and Selectfluor™ (1.1 eq) in dried acetonitrile (150 ml) was placed in a two necked flask with a reflux condenser attached to an Argon line. Reaction mixture was refluxed at 82°C and stirred for 12-18 h. Progression of the reaction was monitored by ^{19}F NMR. After termination of the reaction, the cooled reaction mixture was poured into water (250 ml), extracted with 3 portions of dichloromethane (100 ml) and dried with $MgSO_4$. After filtration, solvent was evaporated at reduced pressure using rotatory evaporator and if necessary, additionally on a vacuum line.

Purification was achieved by column chromatography, distillation by Kugelrohr or precipitation.

6.4 Fluorination of ethers using elemental fluorine

1. Attempted fluorination of diethyl ether (1)

Elemental fluorine was passed through a solution of diethyl ether **(1)** (4 g, 83 mmol) in acetonitrile (150 ml) at 0°C. Due to the high reactivity of the substrate, the reaction started to be very violent, therefore was immediately stopped and no further investigation was attempted.

2. Fluorination of the *n*-dipropyl ether (2)

Elemental fluorine (88.2 mmol, 50 ml min^{-1}) was passed through a solution of n-dipropyl ether **(2)** (3 g, 29.4 mmol) in dry acetonitrile 0°C. The mixture was poured into water and extracted with dichloromethane (3×100 ml). The organic phase was dried with magnesium sulfate.

The ^{19}F NMR of the crude product shows the presence of component consistent with 2-fluoro-1-(2-fluoro-1-propoxy-propoxy)-dipropyl ether **(3)** and δ_F −184.7 (m) α-fluoro-dipropyl ether **(4)** δ_F −127.1 (dt, $^2J_{HF}$ 53.8, $^3J_{HF}$ 9.2) in ratio 1.9:1 and many other mono- and polyfluorinated products in conversion 69%. Purification by column chromatography gave **2-fluoro-1-(2-fluoro-1-propoxy-propoxy)-dipropyl ether (3)** as a mixture of diastereoisomers (0.89 g, 29%), b.p. 30°C at 20 mbar; ν_{max}(film)/cm^{-1}: 2961.2 (C-H); 1079.3 (-O-C-); δ_F (200 MHz, $CDCl_3$): −184.7 (1F, ddq, $^2J_{HF}$ 44.7, $^3J_{HF}$ 21.6, $^3J_{HF}$ 7.5, -O-CH-CH*F*-); δ_H (200 MHz, $CDCl_3$): 4.53 (1H, t, $^3J_{HF}$ 7.5, O-C*H*-CHF-), 4.26 (2H, m, O-CH_2-), 3.63 (1H, m, -C*H*F-), 2.24 (2H, m, -CH_2-CH_2-CH_3), 0.91-1.37 (6H, m, CH_3); δ_c (200 MHz, $CDCl_3$): 101.6 (d, $^2J_{C\text{-}F}$ 26.7, -*C*H-CHF-CH_3), 88.4 (d, $^1J_{C\text{-}F}$ 171.2, -CH-*C*HF-CH_3), 68.1 (s, -*C*H_2-CH_2CH_3), 21.1 (s, CH_2-*C*H_2-CH_3) 14.2 (d, $^2J_{C\text{-}F}$ 21.0, -CH_2-CHF*C*H_3), 8.7 (s, -CH_2-CH_2-*C*H_3); m/z (CI^+) 254 (M^+, required $C_{12}H_{24}F_2O_3$ 254, 2), 196 (76), 159 (69), 93 (100).

3. Fluorination of *n*-dibutyl ether (5)

(1) Elemental fluorine (46.8 mmol) was passed through a solution of *n*-dibutyl ether **(5)** (3.0 g, 23.4 mmol) in acetonitrile at 0°C. The reaction mixture was poured into water (200 ml) and neutralized ($NaHCO_3$). The organic phase was extracted with dichloromethane, dried with $MgSO_4$ and evaporated to give a dark brown crude product (3.6 g).^{19}F NMR of the reaction mixture showed the presence of two main products 1-fluorodibutyl-ether **(7)** −124.2 (dt, $^2J_{H\text{-}F}$ 67.3, $^3J_{H\text{-}F}$ 15.4) and 2-fluoro-1-(2-fluoro-1-butoxy-butoxy)-dibutyl ether **(6)** −196.5 (m) in ratio 1:3.7 in conversion 57%. Purification by column chromatography with eluent: hexane/dichloromethane (20:1) gave only **2-fluoro-1-(2-fluoro-1-butoxy-butoxy)-dibutyl ether (6)** as a colorless liquid (1.07 g, 31%), bp. 86°C at 10 mbar; (Found; C, 62.1; H, 10.0. $C_8H_{32}F_2O_3$ required C, 61.9; H, 10.3%); ν_{max}(film)/cm^{-1}: 2961.3 (C-H); 1079.3 (-O-C); δ_F (200 MHz, $CDCl_3$): −196.5 (m,-CHF-); δ_H (200 MHz, $CDCl_3$): 4.47 (2H m, -O-C*H*$_2$-), 4.29 (1H, m, -C*H*-CHF-) 3.63 (1H, m, -C*H*F-), 3.42 (2H, m, -CH-CHF-C*H*$_2$-CH_3), 1.64 (2H, m, O-CH_2-C*H*$_2$-), 1.41 (2H, m, -CH_2-CH_2-C*H*$_2$-CH_3), 0.98 (3H, t, $^3J_{H\text{-}H}$ 7.6, -O-CH_2-CH_2-CH_2-C*H*$_3$), 0.87 (3H, t, $^3J_{H\text{-}H}$ 7.9, -CHF-CH_2-C*H*$_3$); δ_c(75 MHz, $CDCl_3$): 101.1 (d, $^2J_{C\text{-}F}$ 26.0, -*C*H-CHF-), 95.8 (d, $^1J_{C\text{-}F}$ 172.7, -*C*HF-), 66.2 (s,-O-*C*H_2-), 32.2 (s, O-CH_2-*C*H_2-), 23.6 (d, $^2J_{C\text{-}F}$ 20.5, -CHF-*C*H_2-CH_3), 19.5 (s, -CH_2-*C*H_2-CH_3), 14.0 (s,-CH_2-CH_2-*C*H_3), 9.4 (d, $^3J_{C\text{-}F}$ 4.4, -CHF-CH_2-*C*H_3); m/z (CI$^+$): 310 (M+, $C_{16}H_{32}F_2O_3$ requires 310, 90%), 238 (92), 90 (100).

(2) Elemental fluorine (69.1 mmol) was passed through a solution of *n*-dibutyl ether (2.5 g, 22.3 mmol) in acetonitrile at 0°C. ^{19}F NMR of the reaction mixture showed presence of main products 1-fluorodibutyl ether −124.2 (dt, $^2J_{H\text{-}F}$ 67.3, $^3J_{H\text{-}F}$ 15.4). The reaction mixture was poured into water (200 ml) and neutralized ($NaHCO_3$). The organic phase was extracted with dichloromethane, dried with $MgSO_4$ and evaporated to give a dark brown crude product (2.6 g). ^{19}F NMR spectrum of the reaction mixture showed presence of many products but the two main products were 1-fluorodibutyl-ether and 2-fluoro-1-(2-fluoro-1-butoxy-butoxy)-butyl ether in ratio 1:4.1 in conversion 78%. Purification by column chromatography with eluent hexane/dichloromethane (20:1) gave only 2-fluoro-1-(2-fluoro-1-butoxy-butoxy)-dibutyl ether as a colorless liquid (0.77 g, 38%); Spectral data as above.

(3) Elemental fluorine (69.1 mmol) was passed through a solution of *n*-dibutyl ether (3.0 g, 23.4 mmol) in acetonitrile at 0°C. After 3 hours, the reaction mixture was poured into water

(200 ml). The organic phase was extracted with dichloromethane, dried with $MgSO_4$ and evaporated to a give dark brown crude product (2.6 g). The ^{19}F NMR of the crude product showed presence of two main products 1-fluorodibutyl ether −124.2 (dt, $^2J_{H\text{-}F}$ 67.3, $^3J_{H\text{-}F}$ 15.4) and 2-fluoro-1-(2-fluoro-1-butoxy-butoxy)-dibutyl ether −196.5 (m) in ratio 1:4.9 in conversions 73%. Purification by column chromatography gave only 2-fluoro-1-(2-fluoro-1-butoxy-butoxy)- dibutyl ether as a colorless liquid (1.07 g, 49%); Spectral data as above.

4. Fluorination of *n*-dipentyl ether (8)

Elemental fluorine (38 mmol) was passed through a solution of *n*-dipentyl ether **(8)** (2 g, 12.6 mmol) in acetonitrile (150 ml). After completion of the reaction, the reaction mixture was poured into water (200 ml). The organic phase was extracted with dichloromethane, dried with $MgSO_4$ and evaporated to give a dark brown crude product (3.6 g). Purification by column chromatography with eluent: hexane/dichloromethane. The ^{19}F NMR spectrum of the crude product showed the main product is **2-fluoro-1-(2-fluoro-1-pentyloxy-pentyloxy)-dipentyl ether (9)** (1.04 g, yield 43%) and 4 other fluorinated products in conversion 56%. b.p. 82°C at 4-5 mbar (Found: C, 65.8; H, 10.8. $C_8H_{12}F_2O_3$ requires C, 65.5; H, 11.1%): ν_{max}(film)/cm^{-1}: 2911.9 (C-H); 1061.3 (-O-C-); δ_F (200 MHz, $CDCl_3$): −186.3 (m); δ_H (200 MHz, $CDCl_3$): 4.49 (1H, dd, $^3J_{HF}$ 21.7, $^3J_{HH}$ 17.7, -C*H*-CHF-CH_2-CH_3), 3.62 (2H, t, $^3J_{HH}$ 7.9, O-C*H*$_2$-), 3.37 (1H, m, -CH-C*H*F-CH_2-CH_3), 1.41 (4H, m, -CH-CHF-C*H*$_2$-, O-CH_2-C*H*$_2$-), 1.24 (2H, m, O-CH_2-CH_2-C*H*$_2$-), 1.17 (2H, m, -CH_2-CH_2-C*H*$_2$-CH_3), 0.89 (6H, m, CH_3); δ_c (200 MHz, $CDCl_3$): 102.9 (d, $^2J_{C\text{-}F}$ 26.3, -*C*H-CHF-CH_2-), 95.1 (d, $^1J_{C\text{-}F}$ 172.7, -O-CH-*C*HF-), 68.9 (O-*C*H$_2$), 32.1 (d, $^2J_{C\text{-}F}$ 18.2, CHF-*C*H$_2$), 29.2 (s,-O-CH_2-*C*H$_2$), 28.6 (s, -*C*H$_2$-CH_2-CH_3), 22.7 (s, CH_2-*C*H$_2$-CH_3), 18.4 (d, $^3J_{C\text{-}F}$ 3.7, -CH-CHF-CH_2-*C*H$_2$-CH_3), 14.0 (s, CHF-CH_2-CH_2-*C*H$_3$), 6.7 (s, CH_2-CH_2-*C*H$_3$); m/z(CI$^+$): 366 (M^+, $C_{20}H_{40}F_2O_3$ required 366, 31), 280 (100), 104 (100).

5. Fluorination of the methylbutylether (10)

Elemental fluorine (135 mmol) was passed through a solution of methylbutylether **(10)** (3 g, 269 mmol) in acetonitrile (150 ml). After completion of the reaction, the reaction mixture was poured into water (200 ml) and neutralized ($NaHCO_3$). The organic phase was

extracted with dichloromethane, dried with $MgSO_4$ and evaporated to give a dark brown crude product (2.8 g). The ^{19}F NMR spectrum and GC of the crude product showed thr presence of more than 15 products. Purification by column chromatography was not successful and the reaction was not investigated any further.

6. Fluorination of the isopropyl ether (11)

Elemental fluorine (88.2 mmol, 50 $mlmin^{-1}$) was passed through a solution of isopropyl ether **(11)** (3 g, 29.4 mmol) in acetonitrile (150 ml). After completion of the reaction, the reaction mixture was poured into water (200 ml) and neutralized ($NaHCO_3$). The organic phase was extracted with dichloromethane, dried with $MgSO_4$ and evaporated to give a dark brown crude product (2.67 g). The ^{19}F NMR spectrum and GC of the crude product showed the presence of more than 10 products.

7. Fluorination of *n*-isoamyl ether (12)

Elemental fluorine (47.4 mmol) was passed through a solution of *n*-isoamyl ether **(12)** (2.5 g, 15.7 mmol) in acetonitrile (150 ml). After completion of the reaction, the reaction mixture was poured into water (200 ml) and neutralized ($NaHCO_3$). The organic phase was extracted with dichloromethane, dried with $MgSO_4$ and evaporated to give a dark brown crude product (2.6 g). The ^{19}F NMR spectrum of the crude product showed presence of many mono and polyfluorinated products in 46% conversion. Purification by column chromatography with eluent: hexane/dichloromethane gave the main product as **2-fluoro-1-[2-fluoro-3-methyl-1-(3-methyl-butoxy)-butoxy]-isoamyl ether (13)** (0.9 g, 41%) bp. 83 at 9 mbar; ν_{max}(film)/cm^{-1}: 2954.1 (C-H); 1086.7 (-O-C); δ_F (200 MHz, $CDCl_3$): −206.5 (m,-CHF-); δ_H (200 MHz, $CDCl_3$): 4.48 (1H, dd, $^3J_{HF}$ 7.9, $^3J_{HH}$ 6.3, -O-C*H*-), 4.25 (1H, ddd, $^2J_{HF}$ 47.2, $^3J_{HH}$ 6.3, $^3J_{HH}$ 3.6, -C*H*F-) 3.67 (2H, dt, $^3J_{HH}$ 9.4, $^4J_{HH}$ 6.8, O-CH_2-), 1.93 (1H, dm, $^3J_{HF}$ 28.7, -CH-CHF-C*H*-CH_3), 1.66 (1H, m, O-CH_2-CH_2-CH), 1.45 (2H, m, O-CH_2-CH_2-CH-), 0.9 (6H, d $^3J_{H\text{-}H}$ 7.6, -O-CH_2-CH_2-CH-(CH_3)$_2$), 0.8 (3H, t, $^3J_{H\text{-}H}$ 7.9, -CHF-CH_2-(CH_3)$_2$); δ_c(200 MHz, $CDCl_3$): 101.7 (d, $^2J_{C\text{-}F}$ 26.5, O-*C*H-CHF-), 96.8 (d, $^1J_{C\text{-}F}$ 170.4, -*C*HF-), 66.2 (s,-O-CH_2-), 32.2 (s, O-CH_2-CH_2-), 23.6 (d, $^2J_{C\text{-}F}$ 20.5, -CHF-*C*H-CH_3), 19.5 (s, -CH_2-CH_2-CH_3), 14.0 (s,-CH_2-CH_2-*C*H_3), 9.4 (d, $^3J_{C\text{-}F}$ 4.4, -CHF-CH-*C*H_3); m/z(Cl^+):

310 (M+, $C_{16}H_{32}F_2O_3$ require 310, 90%), 238 (92), 90 (100); Accurate mass: Found 310.3181 (M^+, requires 310.3153)

8. Fluorination of tetrahydrofuran (14)

Elemental fluorine (177 mmol) was passed through a solution of tetrahydrofuran (**14**) (4.25 g, 58 mmol) in acetonitrile (150 ml). After completion of the reaction, the reaction mixture was poured into water (200 ml) and neutralized ($NaHCO_3$). The organic phase was extracted with dichloromethane, dried with $MgSO_4$ and evaporated to give a dark brown crude product (3.6 g). Purification by column chromatography with eluent: hexane/ dichloromethane. The ^{19}F NMR spectrum of the crude product showed that the main product is **3-fluoro-2-(3-fluoro-tetrahydrofuran-2-uloxy)-tetrahydrofuran (15)** (1.1 g, 34%) in 69% conversion; The ratio of the major and minor stereoisomer is 1.63: 1. (Found: C, 48.7; H, 6.1; $C_8H_{12}F_2O_3$ requires: C, 48.7; H, 6.2%). ν_{max} (film)/cm^{-1}: 2961.5 (C-H) 1098.8 (cyclic ether);

Major: δ_F: −185.2 (m) δ_H (200 MHz, $CDCl_3$): 5.26 (1H, m, O-C*H*O-CHF), 5.13 (2H, t, $^3J_{HH}$ 5.7 O-CH_2-CH_2), 4.02 (1H, m O-C*H*O-CHF), 1.98 (2H, m, O-CH_2-CH_2); δ_c (200 MHz, $CDCl_3$): 101.5 (d, $^2J_{C\text{-}F}$ 33.3, O-*C*HO-), 97.3 (d, $^1J_{C\text{-}F}$ 178.1, -*C*HF-), 66.9 (s, O-*C*H_2-CH_2), 30.4 (d, $^2J_{C\text{-}F}$ 20.8, O-CH_2-*C*H_2-) m/z (CI^+): 213 (M-NH_4^+. $C_8H_{12}O_3F_2$-NH_4^+ requires 213, 6), 212 (95), 195 (M^+, $C_8H_{12}O_3F_2$ requires 195, 6), 106 (79), 89 (33).

Minor: δ_F (200 MHz, $CDCl_3$): −184.6 (m); δ_H (200 MHz, $CDCl_3$): 5.29 (1H, m, O-C*H*O-CHF), 5.11 (2H, t, $^3J_{HH}$ 5.7 O-CH_2-CH_2), 4.07 (1H, m O-C*H*O-CHF), 2.02 (2H, m, O-CH_2-CH_2); δ_c (200 MHz, $CDCl_3$) 104,5 (d, $^2J_{C\text{-}F}$ 33.3, O-*C*HO-), 97.2 (d, $^1J_{C\text{-}F}$ 178.1, -*C*HF-), 66.2 (s, O-*C*H_2-CH_2), 30.3 (d, $^2J_{C\text{-}F}$ 20.83, O-CH_2-*C*H_2-) m/z (CI^+): 213 (M+NH_4^+. $C_8H_{12}O_3F_2$-NH_4 requires 213, 6), 212 (95), 195 (M^+, $C_8H_{12}O_3F_2$ requires 195, 6), 106 (39), 89 (18).

9. Synthesis of 1-butoxy-2,4-dinitro-benzene (16)

Sodium (0.57 g, 25 mmol) was added to butanol (20 mmol, 11.3 ml) and dissolved. **1-Chloro-2,4-dinitro-benzene** (5 g, 25 mmol) was dissolved in THF and added slowly via a dropping funnel to the reaction mixture. The reaction was stirred for 8 h at room temperature. The reaction mixture was poured into water, extracted by dichloromethane

(3×100 ml), dried with $MgSO_4$ and evaporated to give a brown oil as a crude product (6.2 g) in 81% conversion. Purification by column chromatography over silica-gel using hexane: DCM 15:1 gave **1-butoxy-2,4-dinitro-benzene (16)** (4.6 g, 100%) as a colorless oily liquid; (Found C, 50.2; H, 5.0; N, 11.7. $C_{10}H_{12}N_2O_5$ requires C, 50.0; H, 5.0; N,11.6%) ν_{max}(film)/cm^{-1}: 2961,1 (C-H), 1538,2 (-NO_2), 1344 (aryl-o-), 1068.8 (alkyl-O-); δ_H (200 MHz, $CDCl_3$): 8.71 (1H, d, $^3J_{H\text{-}H}$ 2.7, H-3), 8.26 (1H, d, $^3J_{H\text{-}H}$ 9.2, $^3J_{H\text{-}H}$ 2.7, H-5), 7.27 (1H, d, $^3J_{H\text{-}H}$ 9.3, H-6), 4.28 (2H, t, $^3J_{H\text{-}H}$ 6.2, CH_2O), 1.82 (2H, m, $CH_3CH_2CH_2$), 1.54 (2H, m, CH_3CH_2), 0.91 (3H, t, $^3J_{H\text{-}H}$ 7.4, CH_3); δ_C (75 MHz, $CDCl_3$): 157.2 (s, C_1), 140.6 (s, $C_{2,4}$), 129.2 (s, C_6), 122.0 (s, C_3), 114.5 (s, C_5), 70.8 (s, CH_2O), 30.8 (s, $CH_3CH_2CH_2$), 19.2 (s, CH_3CH_2), 13.8 (s, CH_3); m/z (EI^+): 241.1 (M^+. $C_{10}H_{12}N_2O_5$ requires 241.5, 32), 183.9 (36), 167.6 (50), 55.8 (98). (As literature data [156]).

10. Direct fluorination of 1-butoxy-2,4-dinitro-benzene (16)

Elemental fluorine (14 mmol, 20 $mlmin^{-1}$) was passed through a solution of 1-butoxy-2,4-dinitro-benzene **(16)** (1 g, 42 mmol) in dry acetonitrile at 0°C. After the completion of the reaction, the mixture was poured into water and extracted with dichloromethane (3×100 ml). The organic phase was dried with magnesium sulfate and evaporated to give a crude product as a brown oil (0.97 g) in 81% conversion. The crude product was purified by column chromatography over silica gel to give **1-butoxy-6-fluoro-2,4-dinitro-benzene (17)** (0.78 g, 90%) as a dark orange oil (Found: C, 54.0; H, 3.9; N, 27.1. $C_{10}H_{11}FN_2O_5$ required C, 53.7; H, 3.7; N, 26.8%); ν_{max}(film)/cm^{-1} 2962.72 (C-H), 1547.67 (-NO_2), 1239.2(-F). δ_F (200 MHz, $CDCl_3$): −121.0 (d, $^3J_{HF}$ 9.8); δ_H (200 MHz, $CDCl_3$): 8.90 (1H, s, H-3), 8.22 (1H, dd, $^3J_{HF}$ 9.8, $^4J_{HH}$ 1.9, H-5), 4.37 (2H, m, -CH_2O), 1.75 (2H, m, $CH_3CH_2CH_2$), 1.55 (2H, m, CH_3CH_2), 0.91 (3H, t, $^3J_{HH}$ 7.4, CH_3); δ_C (75 MHz, $CDCl_3$): 154.8 (d, $^1J_{CF}$ 254.1, C-6), 146.9 (d, $^2J_{CF}$ 13.5, C1), 143.3 (d, $^4J_{CF}$ 3.5, C-3), 142.1 (d, $^3J_{CF}$ 7.6, C-4), 140.8 (d, $^3J_{CF}$ 8.7, C-2), 117.2 (d, $^2J_{CF}$ 17.5, C5), 76.5(d, $^4J_{CF}$ 8.1, -O-CH_2), 32.0 (s, -O-CH_2-CH_2-), 18.9 (s, -CH_2-CH_3), 13.8 (s, -CH_3); m/z (EI^+): 258 (M^+ , $C_{10}H_{11}FN_2O_3$ require 258.0, 2.0), 201.9 (16), 185.7 (32.2), 55.9 (98).

11. Fluorination of 1-butoxy-2,4-dinitro-benzene (16)

Elemental fluorine (8 mmol, 20 ml/min) was passed through solution of butoxy-2,4-dinitro-benzene **(16)** (0.220 g, 1 mmol) in dry acetonitrile at 0°C for 2 h and 30 min. The mixture was poured into water and extracted with dichloromethane (3×100 ml). The organic phase was dried with magnesium sulfate. After evaporation, crude product (conv. 100%) was purified by column chromatography over silica gel to give two products:

1-butoxy-6-fluoro-2,4-dinitro-benzene: (0.14 g, 67%) spectral data same as **(17)**.

and: **1-(α-fluoro)-butoxy-6-fluoro-2,4-dinitro-benzene (18)** (49mg, 23%) δ_F (200 MHz, $CDCl_3$): −118.2 (1F, dd, $^5J_{F\text{-}F}$ 13.7, $^5J_{H\text{-}F}$ 9.6, Ar-F), −124.3 (1F, ddt, $^2J_{H\text{-}F}$ 60.8, $^3J_{H\text{-}F}$ 18.1 $^5J_{F\text{-}F}$ 13.7, CHF) δ_H (200 MHz, $CDCl_3$): 8.43 (1H, d, $^4J_{HF}$ 1.9, H-3), 8.17 (1H, d, $^3J_{HF}$ 9.5, H-5), 5.65 (1H, dt, $^2J_{HF}$ 60.8, $^3J_{HH}$ 3.4 *–O-CHF*), 1.98 (2H, m, -*CH*$_2$-CH_2-CH_3) 1.25 (2H, m, -*CH*$_2$ -CH_3) 0.90 (3H, t, $^3J_{HH}$ 7.0 -*CH*$_3$); δ_C (75 MHz, $CDCl_3$): 149.6 (d, $^1J_{CF}$ 251.1, C-6), 145.9 (d, $^2J_{CF}$ 13.9, C1), 142.1 (d, $^3J_{CF}$ 8.5, C-4), 137.8 (d, $^3J_{CF}$ 8.7, C-1), 117.2(d, $^2J_{CF}$ 15.2, C-5),114.2 (d, $^4J_{CF}$ 2.1 C-3), 102.5 (dd, $^1J_{CF}$ 258.1, $^4J_{CF}$ 8.1, -O-*CH*$_2$), 39.0 (d, $^2J_{CF}$ 22.9, -O-CH_2-*CH*$_2$-), 18.9 (d, $^3J_{CF}$ 7.4, -*CH*$_2$-CH_3), 13.8 (d, $^4J_{CF}$ 1.6, -*CH*$_3$); m/z (EI$^+$): 276 (M^+ required 276.1, 2), 201.9 (5), 74.9 (100), 55.0 (77);

6.5 Fluorinations of ethers with Selectfluor™

1. Fluorination of *n*-dipropyl ether (2)

n-Dipropyl ether **(2)** (2.0 g 19.6 mmol) and Selectfluor™ (7.65 g, 21.5 mmol) were refluxed in acetonitrile (150 ml) for 18 h. The reaction mixture was added to the water and the organic phase was extracted with DCM and dried with $MgSO_4$. The crude product was obtained as brown liquid (1.61 g) and purified by Kugelrohr distillation to give 2-fluoro-1-(2-fluoro-1-propoxy-propoxy)-dipropyl ether **(3)** (1.1 g, 63%) in conversion 72%; spectral data as above.

2. Fluorination of *n*-dibutyl ether (5)

(1) *n*-Dibutyl ether **(5)** (3.31 g, 25.8 mmol) and Selectfluor™ (10.0 g, 28.1 mmol, 1.1eq.) were refluxed in acetonitrile (150 ml). ^{19}F NMR spectrum of the reaction mixture shows the presence of α-fluoro-dibutyl ether **(7)**, δ_F −124.1 (dt, $^2J_{HF}$ 45.8, $^3J_{HF}$ 8.2) and 2-fluoro-1-(2-fluoro-1-butoxy-butoxy)-dibutyl ether **(6)** δ_F −187.3 (m) in ratio 2:1. After 18 h, the reaction mixture was poured into water (200 ml) and neutralized ($NaHCO_3$). Organic phase was extracted with DCM and dried with $MgSO_4$. The crude product was obtained as a brown liquid (3.01 g) in conversion 67% and purified by column chromatography over silica gel (20g). Purification by column chromatography gave only 2-fluoro-1-(2-fluoro-1-butoxy-butoxy)-dibutyl ether as a colorless liquid (1.07 g, 72%). (Spectral data as above)

(2)A *n*-dibutyl ether **(5)** (3.0 g 23.4 mmol) and Selectfluor™ (5.0 g, 25.7 mmol) were refluxed in acetonitrile (150 ml) for 18 h. The reaction mixture was poured into water, extracted with DCM and dried with $MgSO_4$. The crude product was obtained as a brown liquid (2.8 g) in conversion (72%) and purified by column chromatography to give 2-fluoro-1-(2-fluoro-1-butoxy-butoxy)-dibutyl ether (1.4 g, 81%) as a colorless oil. (Spectral data as above)

(3) A *n*-dibutyl ether **(5)** (3.0 g 23.4 mmol) and Selectfluor™ (5.0 g, 25.7 mmol) were refluxed in wet acetonitrile (150 ml) for 18 h.^{19}F NMR spectrum reaction mixture show presence of one main product 2-fluoro-1-(2-fluoro-1-butoxy-butoxy)-dibutyl ether δ_F −184.7 (m) in ratio 1:6.1. The reaction mixture was poured in to the water, extracted with DCM and dried with $MgSO_4$. The crude product was obtained as brown liquid (2.8 g) in conversion (69%) and purified at column chromatography to give product 2-fluoro-1-(2-fluoro-1-butoxy-butoxy)-dibutyl ether (1.2 g, 78%). (Spectral data as above)

3. Fluorination of *n*-dipentyl ether (7)

A solution of Selectfluor™ (7.4 g, 17 mmol) and dipentyl ether **(7)** (2.4 g, 15 mmol) in dry acetonitrile was refluxed at 82°C for 18 h. After the reaction, the mixture was poured into water and extracted with dichloromethane (3×100 ml). Organic phase was dried with magnesium sulfate. ^{19}F NMR spectrum of the crude product shows the presence of the main product 2-Fluoro-1-(2-fluoro-1-pentyloxy-pentyloxy)-dipentyl ether **(8)** (2.37 g, 54%) in conversion 62%. Pure product was isolated by preparative TLC. (Spectral data as above).

4. Fluorination of isoamyl ether (12)

(1) A solution of Selectfluor™ (3.8 g, 8 mmol) and isoamyl ether **(12)** (1.2 g, 7 mmol) in dry acetonitrile was refluxed at 82°C for 18 h. After the reaction, the reaction mixture was poured into water and extracted with dichloromethane (3×100 ml). Organic phase was dried with magnesium sulfate. The ^{19}F NMR spectrum of the crude product showed the presence of many mono and polyfluorinated products. Only the main product was isolated by preparative TLC as 2-Fluoro-1-[2-fluoro-3-methyl-1-(3-methyl-butoxy)-butoxy]-isoamyl ether **(13)** (0.76 g, 56%) in conversion 62%; (Spectral data as above).

(2) The solution of the Selectfluor™ (3.8 g, 8 mmol) and isoamyl ether **(12)** (1.2 g, 7 mmol) in wet acetonitrile was refluxed 82°C at for 40 h. The ^{19}F NMR spectrum of the reaction mixture showed presence of only 2-Fluoro-1-[2-fluoro-3-methyl-1-(3-methyl-butoxy)-butoxy]-isoamyl ether **(13)**. The reaction mixture was poured into water and extract with dichloromethane (3×100 ml). Organic phase was dried with magnesium sulfate. The ^{19}F NMR spectrum of the crude product showed presence of 3 fluorinated products in conversion 49%. The crude product was purified by preparative TLC to give 2-Fluoro-1-[2-fluoro-3-methyl-1-(3-methyl-butoxy)-butoxy]-isoamyl ether (0.76 g. 63%) as a colorless liquid; (Spectral data as above).

5. Fluorination of tetrahydrofuran (14)

The solution of the Selectfluor™ (7 g, 20 mmol) and tetrahydrofuran **(14)** (1.29 g, 18 mmol) in dry acetonitrile was refluxed at 62°C for 18 h. After 16 h, the reaction mixture was poured into the water and extracted with dichloromethane (3×100 ml). Organic phase was dried with magnesium sulfate and evaporated to give a crude product (1.15 g) in conversion 91%. After evaporation, the crude product was purified by Kugelrohr distillation 3-fluoro-2-(3-fluoro-tetrahydrofuran-2-uloxy)-tetrahydrofuran **(15)** (0.71 g, 90%) was isolated as a mixture of diastereoisomers; (Spectral data as above).

6. Fluorination of 3-fluoro-2-(3-fluoro-tetrahydrofuran-2-uloxy)-tetrahydrofuran (15)

The solution of the Selectfluor™ (2.8 g, 8 mmol) and 3-fluoro-2-(3-fluoro-tetrahydrofuran-2-uloxy)-tetrahydrofuran **(15)** (1.54 g, 7 mmol) in dry acetonitrile was refluxed at 62°C for

36 h. The reaction did not resulted in formation of new product. Negligible amount of fluorine of the tar was formed.

7. Fluorination of 1-butoxy-2,4-dinitro-benzene (16)

A mixture of Selectfluor™ (1.6 g, 4.5 mmol) and butoxy-2,4-dinitro-benzene **(16)** (1.1 g, 4.2 mmol) was heated on reflux temperature in dry acetonitrile for 16 hours. No reaction was observed by ^{19}F NMR and GC.

Chapter 7 Experimental to chapter 3

3.1 Fluorination of deactivated benzene derivatives using elemental fluorine

1. Fluorination of 2,4-dinitrotoluene (19)

(1) Elemental fluorine (3eq. 16 mmol) was passed through a solution of 2,4-dinitro toluene **(19)** (1 g, 5.5 mmol) in dry acetonitrile (150 ml). Reaction mixture was poured into water (150 ml), neutralized with $NaHCO_3$ and the organic part was extracted with dichloromethane (3×100 ml) and dried with $MgSO_4$. The crude product (1.3 g) was isolated in 19% conversion and purification by preparative TLC (1:1 hexane:ethyl acetate as eluent) gave pure **6-fluoro-2,4-dinitrotoluene (20)** (0.28 g, 100%) as a yellow oil, (Found: C, 42.3; H, 2.7; N, 13.9. $C_7H_5FN_2O_4$ requires: C, 42.0; H, 2.5; N, 14.0%). δ_F (300 MHz, $CDCl_3$): −106.3 (d, $^3J_{HF}$ 8.3); δ_H (200 MHz, $CDCl_3$): 8.72 (1H, s, H-3), 8.14 (1H, dd, $^3J_{HF}$ 8.3, $^4J_{HH}$ 2.4, H-5), 2.48 (3H, d, $^4J_{HF}$ 2.1 CH_3); δ_c (125 MHz, $CDCl_3$) 161.0 (d, $^1J_{CF}$ 252.2, C-6), 150.1 (s, C-3), 146.0 (d, $^3J_{CF}$ 9.8, C-4), 129.2 (d, $^2J_{CF}$ 20.8, C-5), 115.5 (d, $^3J_{CF}$ 3.8, C-2), 114.6 (d, $^2J_{CF}$ 28.9, C-1), 11.7 (d, $^3J_{CF}$ 4.9, CH_3); m/z(EI^+) 200 (M^+, $C_7H_5FN_2O_4$ requires 200.0, 10.9), 183 (100), 107 (82). (as literature data [54])

(2) Elemental fluorine (9eq. 49.0 mmol) was passed through a solution of 2,4-dinitro toluene **(19)** (1 g, 5.5 mmol) in dry acetonitrile (150 ml). After aqueous work-up procedure crude product (1.3 g) was isolated and purified by column chromatography using 15: 1 hexane: ethyl acetate as eluents to give pure product 6-fluoro-2,4-dinitrotoluene **(20)** (conv. 29%, yield. 92%) as yellow oil; (Spectral data as above).

(3) A solution consisting of 2,4-dinitrotoluene **(19)** (1 g, 5.5 mol) and conc. sulfuric acid (100 ml) at -10°C was subjected to a flow elemental fluorine (3eq. 16.5 mmol) at rate 50 $mlmin^{-1}$. The crude product were poured into water (800 ml) with ice and extracted with DCM and dried with $MgSO_4$. Solvent was removed to leave a crude oil (1.2 g). (conv. 2%)

(4) Elemental fluorine (3eq. 16.5 mmol) was passed through cooled (0°C) solution containing 2,4-dinitrotoluene **(19)** (1 g, 5.5 mmol) in sulfuric acid (100 ml). The resulted

mixture was poured into water with ice (800 ml) and extracted by DCM. The combined dried ($MgSO_4$) organic extract was evaporated to give crude product (1.3 g) (conv. 2%).

(5) A solution consisting of 2,4-dinitrotoluene **(19)** (1 g, 5.5 mmol) and conc. sulfuric acid (100 ml) at 15°C was subjected to a flow elemental fluorine (3eq. 16.5 mmol) at rate 50 $mlmin^{-1}$. The crude product were poured into water (800 ml) with ice and extracted with DCM and dried with $MgSO_4$. Solvent was removed to leave a crude oil (1.2 g) (conv. 2.5%).

(6) A solution consisting of 2,4-dinitrotoluene **(19)** (1 g, 5.5 mmol) and conc. formic acid (100 ml) at 0°C was subjected to a flow elemental fluorine (3eq. 16.5 mmol) at rate 50 ml min^{-1}. The crude product were poured onto water (800 ml) with ice and extracted with DCM and dried with $MgSO_4$. Yellow crude oil was isolated (1.17 g); (conv.9%); (Spectral data as above).

(7) Elemental fluorine **(19)** (3eq. 16.5 mmol) was passed through a solution of 2,4-dinitrotoluene (1 g, 5.5 mmol) in mixture of dry acetonitrile (90 ml) and formic acid (30 ml). After aqueous work-up procedure the crude product (1.2 g) was isolated (conv. 9.3%, yield. 100%); (Spectral data as above).

(8) Elemental fluorine (3eq. 42 mmol) was passed through a solution of 2,4-dinitrotoluene **(19)** (2.5 g, 14.0 mmol) in mixture of dry acetonitrile (90 ml) and formic acid (30 ml). After aqueous work-up procedure the crude product (1.2 g) was isolated. (conv. 19.3%, yield. 92%); (Spectral data as above).

(9) Elemental fluorine (3eq., 42 mmol) was passed through a solution of 2,4-dinitrotoluene **(19)** (2.5 g, 14 mmol) in dry acetonitrile (120 ml). After aqueous work-up procedure the crude product (1.2 g) was isolated. (conv. 20%, yield. 100%); (Spectral data as above).

(10) Elemental fluorine (3eq. 140 mmol) was passed through a solution of 2,4-dinitrotoluene **(19)** (5 g, 30 mmol) in dry acetonitrile (120 ml). After aqueous workup procedure crude product (1.2 g) was isolated. (conv. 20%, yield. 98%); (Spectral data as above).

(11) Elemental fluorine (3eq. 210 mmol) was passed through a solution of 2,4-dinitrotoluene **(19)** (7.5 g, 44 mmol) in mixture of dry acetonitrile (120 ml). After aqueous workup procedure the crude product (1.2 g) was isolated. (conv. 22%, yield. 100%)

2. Fluorination of 2,4-dinitroanisole (21)

Elemental fluorine (12 mmol, 3 eq.) was passed through a solution of 2,4-dinitroanisole (0.8 g., 4 mmol) in dry acetonitrile (150 ml). Aqueous work-up gave a dark yellow crude product (0.95 g). Conversion was determined to be 55% purification gave **6-fluoro-2,4-dinitroanisole (22)** (0.32 g, 84%); δ_F (376 MHz, $CDCl_3$) −121.61 (1F, d, $^3J_{HF}$ 9.0); δ_H (200 MHz, $CDCl_3$) 8.52 (1H, m, H-3), 8.23 (1H, dd, $^3J_{HF}$ 10.4, $^4J_{HH}$ 2.4, H-5), 4.23 (3H, s, CH_3), δ_c (75 MHz, $CDCl_3$) 155.0 (d, $^1J_{CF}$ 255.2, C-6), 147.1 (d, $^2J_{CF}$ 13.5, C-1), 143.0 (d, $^3J_{CF}$ 2.8, C-2), 141.2 (d, $^3J_{CF}$ 3.1 C-4), 116.8 (s, C-3), 116.6 (d, $^2J_{CF}$ 22.3, C-5), 62.0 (s, CH_3); m/z (EI^+) 217.1 (M^+, $C_7H_5FN_2O_4$ requires 216, 3), 215.9 (38), 185.9 (100), 94 (68). Accurate mass: Found 216.0181 (M^+, requires 216.0176) (as literature data[157])

3. Synthesis of 2,4-dinitroacetanilide (24)

2,4-Dinitroaniline **(23)** (8.60 g, 0.047 mol) and acetic acid anhydride (10.2 g, 0.1 mol) was dissolved in acetic acid (30 ml) stirred and refluxed for 12 hours. The reaction mixture was afterwards poured into water and the crude product was precipitated, filtered and dried at the air. After purification by column chromatography, **2,4-dinitroacetinilide (24)** (8.7 g, 95%) was isolated as white crystals in conversion 98%. m.p. 78°C, (Found: C. 42.6; H, 3.1; N, 18.8. $C_8H_7N_3O_5$ requires: C, 42.7; H, 3.1; N, 18.7%); ν_{max}(film)/cm^{-1}: 3323.0; 2357.4; 1697.3; 1593.4; 1495.6; 1330.6; δ_H (200 MHz,$CDCl_3$) 10.7 (1H, s, NH), 8.63 (1H, d, $^4J_{HH}$ 2.7, H-3), 8.47 (1H, dd, $^3J_{HH}$ 9.0, $^4J_{HH}$ 2.7, H-5), 7.91 (1H, d, ^3J 9.3, H-6), 2.09 (3H, s, CH_3); δ_c (125 MHz,$CDCl_3$): 169.6 (s, C=O), 143.0 (s, C-4), 141.2 (s, C-2), 137.5 (s, C-1), 129.2 (s, C-3), 125.6 (s, C-6), 121.8 (s, C-5), 24.4 (s, CH_3); m/z(EI^+) 226.1 (M^+ $C_8H_7N_3O_5$ requires 225.6, 54), 167(100), 121(86). Accurate mass: Found 225.0384 (M^+, requires 225.0386) (as literature data [158])

4. Fluorination of 2,4-dinitroacetinilide (24)

Elemental fluorine (37.3 mmol) was passed through a solution of 2,4-dinitroacetinilide **(24)** (2.78 g., 12.3 mmol) in dry acetonitrile. Aqueous work up gave a bright orange solid (3.13 g). Conversion determined to be 22%. The products were 6-fluoro-2,4-dinitroacetinilide **(25)** (64%) and 6-fluoro-N,N-difluoro-2,4-dinitroaniline **(26)** (14%).

Crude product: δ_F (200 MHz, $CDCl_3$) 63.05 (d, $^3J_{FF}$ 20.1, NF_2), 60.33 (s, N-F), −107.40 (d, $^3J_{HF}$ 9.15 F-C6), −109.5 (dt, $^2J_{HF}$ 20.3, $^3J_{FF}$ 9.30, *F*-C6). Ratio: 5.4: 4.5: 10: 2.3: 2.7

6-fluoro-2,4-dinitroacetinilide (25) (64%) δ_F (200 MHz, $CDCl_3$) −107.40 (d, $^3J_{HF}$ 9.15 F-C6); m/z (EI^+) 243 (2, M^+ $C_8H_6FN_3O_5$ requires 243.0, 2) 200.1 (100);

6-fluoro-N,N-difluoro-2,4-dinitroaniline (26): δ_F (200 MHz, $CDCl_3$): 63.0 (2F, d, $^3J_{FF}$ 20.1, 2F, NF_2), −109.4 (1F, dt, $^3J_{FF}$ 20.1, $^3J_{HF}$ 9.8, *F*-6); δ_H (200 MHz, $CDCl_3$): 8.40 (1H, br.s, H-3), 8.32 (1H, d, $^3J_{HF}$ 9.2, H-1); m/z (EI^+) 201.2 (M^+, $C_6H_2F_3N_3O_4$ requires 237)) 199 (100); (as literature data [125]).

5. Fluorination of 2,4-dinitroacetinilide (24)

Elemental fluorine (26.5 mmol) was passed through a solution of 2,4-dinitroacetinilide **(24)** (2.0 g, 8.8 mmol) in sulfuric acid. Aqueous work up gave a bright yellow solid (1.7 g) which was determined to be 2,4-dinitroaniline **(23).**

6. Fluorination of 1-chloro-2,4-dinitro-benzene (27)

Elemental fluorine (4eq. 15 mmol) was passed through a solution of 1-chloro-2,4-dinitro-benzene **(27)** (1 g, 5.0 mmol) in dry acetonitrile (150 ml). After aqueous work up procedure the crude product (1.3 g) was isolated in 45% conversion and purification by preparative TLC (1:1 hexane: ethyl acetate as eluent) gave pure **6-fluoro-2,4 chlorodinitro-benzene (28)** (0.47 g, 95%) as a yellow oil. δ_F (200 MHz, $CDCl_3$) −103.3 (d, $^3J_{HF}$ 7.8); δ_H (200 MHz, $CDCl_3$) 8.54 (1H, dd, $^4J_{HH}$ 3.5, $^5J_{HF}$ 1.4, H-3), 8.11 (1H, dd, $^3J_{HF}$ 7.5, $^4J_{HH}$ 2.4, H-5); δ_c (125 MHz, $CDCl_3$) 160.0 (d, $^1J_{CF}$ 258.2, C-6), 149.0 (s, C-4), 146.0 (s, C2), 123.2 (d, $^2J_{CF}$ 21.8, C-1), 116.5 (d, $^5J_{CF}$ 2.9, C-3), 115.5 (d, $^2J_{CF}$ 26.9, C-5); m/z (EI^+) 223 (M^+, $C_6H_2ClFN_2O_4$ requires 220.02, 8.1), 221.6 (54), 127.7 (100), 92 (98); accurate mass: found 219.9683 (M^+. $C_6H_2ClFN_2O_4$ requires 219.9687) (as literature data [159]).

7. Fluorination of 1-fluoro-2,4-dinitro-benzene (29)

Elemental fluorine (4eq. 47.7 mmol) was passed through a solution of 1-fluoro-2,4-dinitro-benzene **(29)** (1 g, 5.3 mmol) in dry acetonitrile (150 ml). After aqueous work up procedure the crude product (1.3 g) was isolated and purification by preparative TLC (1:1 hexane: ethyl acetate as eluent) gave pure **1,6-difluoro-2,4-dinitro-benzene (30)** (0.17 g, 97%) as a yellow oil in conversion 15.4%. δ_F (300 MHz, $CDCl_3$): −126.0 (dd, $^3J_{FF}$ 20.3, $^3J_{HF}$ 7.7), −129.0 (ddt, $^3J_{FF}$ 20.3, $^4J_{HF}$ 4.5, $^4J_{HF}$ 0.67); δ_H (300 Hz, $CDCl_3$): 8.24 (1H, m, H-3), 8.12 (1H, m, H-5); δ_c (125 Hz, $CDCl_3$): 151.3 (dd, $^1J_{CF}$ 259.1, $^2J_{CF}$ 13.2, C-1), 149.5 (dd, $^1J_{CF}$ 278.1, $^2J_{CF}$ 15.7, C-6), 141.5 (m (br s) , C-2), 137.2 (m, C-4), 117.1 (dd, $^2J_{CF}$ 22.3 , $^3J_{CF}$ 2.3, C-5), 115.2 (t, $^3J_{CF}$ 3.1 C-3); m/z (EI^+) 205.1 (M^+, $C_6H_2F_2N_2O_4$ requires 205.1, 6.1), 203.6 (58), 111.8 (100). Accurate mass: Found 203.9984 (M^+, requires 203.9982)

8. Fluorination of 1,3-dinitro-benzene (31)

Elemental fluorine (5eq. 17.9 mmol) was passed through a solution of 1,3-dinitro-benzene **(31)** (1 g, 6.0 mmol) in dry acetonitrile (150 ml). After aqueous workup procedure, the crude product (1.7 g) was isolated and purification by preparative TLC (1:1 hexane: ethyl acetate as eluent) gave pure **5-fluoro-1,3-dinitrobezene (32)** (0.01 g, 98%) as a yellow oil in 9% conversion; (Found C, 38.6, H, 1.5, N, 14.9. $C_6H_3FN_2O_4$ required: C, 38.7, H, 1.6, N, 15.0 %); δ_F (200 Hz, $CDCl_3$) −103.6 (t, $^3J_{HF}$ 8.4,); δ_H (200 Hz, $CDCl_3$) 8.9 (1H, m, H-2), 8.3 (2H, dd, $^3J_{HF}$ 8.4, $^4J_{HH}$ 2.4, H-4); δ_c (125 Hz, $CDCl_3$) 163.0 (d, $^1J_{CF}$ 292.2, C-5), 156.0 (d, $^3J_{CF}$ 9.8, C-1), 117.5 (d, $^4J_{CF}$ 3.8, C-2), 115.1 (d, $^2J_{CF}$ 28.9, C-4); m/z (EI^+) 186.0 (M^+, $C_6H_3FN_2O_4$ requires 185.0, 73), 169 (5.8), 139 (100). Accurate mass: Found 186.0076 (M^+, requires 216.0077) (as literature data [160])

9. Fluorination of 1,3-dicyano-benzene (33)

(1) Elemental fluorine (23.4 mmol) was passed through solution of 1,3-dicyano-benzene (1 g, 7.81 mmol) in dry acetonitrile. Aqueous work up gave a dark yellow crude product (0.98 g). Conversion was determined to be 10%. The products were **5-fluoroisophthalonitrile (34)** (79 mg, 80%): δ_F (200 Hz, $CDCl_3$): −105.7 (t, $^3J_{HF}$ 6.98); δ_H (200 Hz, $CDCl_3$): 7.78 (1H, m, H-1), 7.67 (2H, dd, $^3J_{HF}$ 6.9, $^4J_{HH}$ 0.2, H-2); m/z (EI^+) 146.1 (M^+, $C_8H_3FN_2$ requires 146, 2), 146.0 (100), 132 (36) 128 (91), 93 (53).

(2) Elemental fluorine (246.10 mmol, 9eq.) was passed through a solution 1,3-dicyanobenezene **(33)** (3.5 g, 27.4 mmol) in dry acetonitrile . Aqueous work up gave a dark yellow crude product (3.46 g). Conversion was determined to be 12% and purification gave 5-Fluoroisophthalonitrile **(34)** (72%); (same as above).

10. Fluorination of 3-nitrobenzonitrile (35)

Elemental fluorine (92 mmol, 3 eq.) was passed through a solution of 3-nitrobenzonitrile **(35)** (5 g, 31 mmol) in dry acetonitrile. Aqueous work up gave a dark yellow crude product (5.21 g). Conversion determined to be 14% and products was **5-fluoro-3-nitrobenzonitrile (36)** (0.57 g, 89%); m.p. 49.3-50.1°C; (Found: C, 49.5; H, 1.8; N, 16.7. $C_7H_5FN_2O_5$ requires C, 50.6; H, 1.8; N, 16.8%); δ_F (300 MHz, $CDCl_3$) −104.8 (1F, d, $^3J_{HF}$ 6.7); δ_H (300MHz, $CDCl_3$) 8.32 (1H, m, *H*-2), 8.13 (1H, dt, $^3J_{HF}$ 6.7, $^4J_{HH}$ 2.4, *H*-6), 7.67 (1H, m, *H*-4); δ_c (125MHz, $CDCl_3$) 164.1 (d, $^1J_{CF}$ 254.3 *C*F), 148.6 (d, $^3J_{CF}$ 5.7, *C*-3), 125.4 (d, $^2J_{CF}$ 22.3, C-6), 123.4 (d, $^4J_{CF}$ 4.3, C-2) 116.4 (d, $^2J_{CF}$ 25.3 C-4), 115.9 (s, C-N), 114.3 (d, $^3J_{CF}$ 7.8, C-1); m/z (EI^+) 183.4 (M^+, $C_8H_7FN_2O_2$ requires 182.3), 182.2 (100), 94 (68). Accurate mass: Found 166.0177 (M^+, requires 166.0178) (as literature data [128])

11. Fluorination of 2,4-dinitrotoluene (19) with selectfluor

Using (1.1 eq, 2.0 g, 6.1 mmol) selectfluor with 2,4-dinitrotoluene **(19)** (1.0 g, 11.1 mmol), reaction was carried out at 82°C in dry acetonitrile. The mixture was poured into water and extracted with dichloromethane (3×100 ml). Organic phase was dried with magnesium sulfate. After evaporation, the crude product was isolated. GC and TLC showed presence of only starting material and no reaction had occurred.

Chapter 8 Experimental to Chapter 4

8.1 Fluorination of the benzaldehyde derivatives using elemental fluorine

1. Fluorination of benzaldehyde (37)

Elemental fluorine (56 mmol, 3 eq.) was passed through a solution of benzaldehyde **(37)** (1.4 g, 13 mmol) in acetonitrile (150 ml). After completion of the reaction, pure nitrogen was purged through the reaction mixture for 15 minutes. ^{19}F NMR of the reaction mixture showed the presence of 2-fluorobenzaldehyde **(38)**; δ_F (ppm) −120.4 (dd, $^3J_{HF}$ 9.48, $^3J_{HF}$ 7.81), 3-fluorobenzaldehyde **(39)**; δ_F (ppm) −111.6 (dd, $^3J_{HF}$ 9.48, $^3J_{HF}$ 7.81), 4-fluorobenzaldehyde **(40)**; δ_F (ppm) −103.3 (dd, $^3J_{HF}$ 9.48, $^3J_{HF}$ 7.81) and benzoyl fluoride **(41)** δ_F (ppm) 20.3 (s) in the ratio 0.9:5.2:1.9:1 in 48% conversion.

3,5-Dinitrobenzyl alcohol was added to the reaction mixture and stirred at room temperature. Pyridine (1 ml) was added and the reaction was stirred for two hours. The reaction mixture was poured into water, extracted by dichloromethane (3×100 ml), dried ($MgSO_4$) and evaporated to give a dark brown crude product. Purification by column chromatography gave **2-fluorobenzaldehyde (38)** (0.14 g, 9%): δ_F (ppm) −120.4 (dd, $^3J_{HF}$ 9.48, $^3J_{HF}$ 7.81); m/z (EI$^+$): 124.0 (M^+, C_7H_6FO requires 124.2), 104.1(100), 77 (72); (as literature data [135])

3-fluorobenzaldehyde (39) (0.84 g. 52%), δ_F (ppm) −111.6 (dd, $^3J_{HF}$ 9.48, $^3J_{HF}$ 7.81); 124.0 (M^+, C_7H_6FO requires 124.2), 104.0(100), 79 (70); (as authentic sample Sigma Aldrich co.).

4-fluorobenzaldehyde (40) (0.34 g. 19%) δ_F (ppm) −103.3 (dd, $^3J_{HF}$ 9.48, $^3J_{HF}$ 7.81); 124.0 (M^+, C_7H_6FO requires 124.2), 104.0(100), 77 (62); (as literature data [130])

5-dinitrobenzyl benzoate (43) (0.29 g, 11%) as a white solid m.p. 164-165°C; (Found: C, 55.6; H, 3.3; N, 9.2. $C_{14}H_{10}N_2O_6$ requires C, 55.3; H, 3.3; N, 9.2%); ν_{max}(KBr)/cm^{-1}: 1733.7 (C=O); 1523.4 (-NO_2); 1339.2; 1272.9 (C-O-); δ_H (300 MHz, $CDCl_3$) 9.03 (1H, t, $^4J_{HH}$ 2.20, 4'-H), 8.66 (2H, d, $^4J_{HH}$ 2.0, 2'-H, 6'-H), 8.08 (2H, dt, $^3J_{HH}$ 7.1, $^4J_{HH}$ 1.2, 2-H), 7.61 (1H, tt,

$^3J_{HH}$ 7.4, $^4J_{HH}$ 1.6, 4-H), 7.50 (2H, tt, $^3J_{HH}$ 7.4, $^4J_{HH}$ 1.17, 3-H), 5.56 (2H, s, CH_2); δ_c (125MHz, $CDCl_3$) 166.1 (s, *C*=O), 149.2 (s, 3-C'), 140.9 (s, 1'-C), 134.0 (s, 4-C), 130.0 (s, 2-C), 129.2 (s, 1-C), 128.9 (s, 2-C') 128.1 (s, 3-C), 118.8 (s, 4'-C), 64.5 (s, CH_2); m/z (EI^+): 302.0 (M^+, $C_{14}H_{10}N_2O_6$ requires 302.2), 104.1(100), 77 (72).

2. Fluorination of 3-nitrobenzaldehyde (45)

Elemental fluorine (45 mmol, 3eq.) was passed through a solution of 3-nitrobenzaldehyde **(44)** ((2.5 g, 15 mmol) in acetonitrile (150 ml). ^{19}F NMR of the reaction mixture showed the presence of 5-fluoro-3-nitrobenzaldehyde **(45)** (19% yield) δ_F (ppm) -103.2 (t, $^3J_{HF}$ 7.8) and 3-nitrobenzoyl fluoride **(46)** (79 % yield); δ_F (ppm) 20.3(s); in the ratio 1: 4.1 in 39% conversion.

3,5-Dinitrobenzyl alcohol was added to the reaction mixture and stirred at room temperature. Pyridine (1 ml) was added and the reaction was stirred for 18 h. The reaction mixture was poured into water, extracted by dichloromethane (3×100 ml), dried ($MgSO_4$) and evaporated to give a dark brown crude product. Purification by column chromatography gave **5-fluoro-3-nitrobenzaldehyde (45)** (0.47 g, 19%) as an orange solid m.p. 47-49°C. (Found C, 49.2; H, 2.4; N, 8.1. $C_7H_5FN_2O_5$ requires C, 49.2; H, 2.3; N, 8.2 %); δ_F (300 MHz, $CDCl_3$) −103.2 (1F, t, $^3J_{HF}$ 7.8); δ_H (300MHz, $CDCl_3$) 10.03 (1H, s, C*H*O), 8.47 (1H, m, 2-H), 8.15 (1H, dt, $^3J_{HF}$ 8.7, $^4J_{HH}$ 2.7, 6-H), 7.95 (1H, m, 4-H); δ_c (125MHz, $CDCl_3$) 188.8 (d, $^4J_{CF}$ 1.9, *C*HO), 164.1 (d, $^1J_{CF}$ 254.3, *C*-F), 149.9 (d, $^3J_{CF}$ 8.14, 3-*C*), 139.1 (d, $^3J_{CF}$ 6.1, 1-C), 121.5 (d, $^2J_{CF}$ 22.4, 6-C), 120.7 (d, $^2J_{CF}$ 3.37, 2-C) 116.9 (d, $^2J_{CF}$ 25.3 4-C); m/z (EI^+) 170.4 (M^+, $C_7H_4FNO_3$ requires 169.3), 140.2 (100), 96 (48). (as authentic sample Aldrich co.).

and **5-dinitrobenzyl-(3-nitro)-benzoate ester (47)** (38 g, 79%) as an orange solid; m.p. 135.4-137.1°C; ν_{max}(KBr)/cm^{-1}: 1719.9 (C=O); 1522.4 (-NO_2); 1332.2; 1282.3 (C-O-); δ_H (300 MHz, $CDCl_3$) 8.95 (1H, t, $^4J_{HH}$ 1.3, 4-H'), 8.88 (2H, dt, $^4J_{HH}$ 0.8, $^4J_{HH}$ 0.4, 2-H', 6-H'), 8.82 (1H, dd, $^3J_{HH}$ 1.8, $^4J_{HH}$ 1.2, 2-H), 8.54 (1H, ddd, $^3J_{HH}$ 7.8, $^4J_{HH}$ 1.8, $^4J_{HH}$ 1.2, 6-H), 5.79 (2H, d, $^4J_{HH}$ 0.4, CH_2), 8.51 (1H, ddd, $^3J_{HH}$ 7.8 $^4J_{HH}$ 1.8, $^4J_{HH}$ 1.2, 4-H), 7.89 (1H, dt, $^3J_{HH}$ 8.0, $^5J_{HH}$ 0.4, 5-H); δ_c (125MHz, $CDCl_3$) 164.2 (s, *C*=O), 148.9 (s, 3-C'), 148.6 (s, 1-C'), 140.6 (s, 3-C), 131.2 (s, 1-C), 135.6 (6, 6-C), 130.7 (s, 5-C), 128.9 (s, 4-C), 128.1 (s, 2-C), 124.3 (s, 2-C'), 118.2 (s, 4-C'), 65.0 (s, CH_2): m/z (EI^+): 347.8 (M^+, $C_{14}H_9N_3O_8$

requires 370, 5) 330.3 (24), 180 (100), 150 (42); accurate mass: Found 370.0287 (M^+, requires 370.0307).

The reaction was repeated using different solvents and results are presented in table below.

Entry	Solvent	T (°C)	Crude product (conv. %)	Yield Ar-F (%)	Yield CFO (%)
1	CH_3CN	0	39	19	79
2	CH_3CN/HCOOH	0	36	25	72
3	HCOOH	0	21	45	51
4	H_2SO_4	15	>1	97	0

3. Fluorination of 3-formylbenzonitrile (48)

Elemental fluorine (57 mmol, 3 eq.) was passed through a solution of 3-formylbenzonitrile **(48)** (2.5 g, 19 mmol) in acetonitrile (150 ml). ^{19}F NMR of the reaction mixture showed the presence of 5-fluoro-3-formylbenzonitrile **(50)** (23 % yield); δ_F (200 MHz, $CDCl_3$) −107.2 (t, $^3J_{HF}$ 7.2) and 3-cyanobenzoyl fluoride **(49)** (75 % yield); δ_F (200 MHz, $CDCl_3$) 17.3 (s); in the ratio 1:3.2 in 34% conversion.

3,5-Dinitrobenzyl alcohol was added to the reaction mixture and stirred at room temperature. Pyridine (1 ml) was added and the reaction was stirred for two hours. The reaction mixture was poured to into water, extracted by dichloromethane (3×100 ml), dried ($MgSO_4$) and evaporated to give a dark brown crude product. Purification by column chromatography gave **5-fluoro-3-formylbenzonitrile (50)** (0.65 g, 23 %) as an orange solid; m.p. 53.6-55.1°C; δ_F (200 MHz, $CDCl_3$) −107.2 (dt, $^3J_{HF}$ 7.7, $^5J_{HF}$ 1.2); δ_H (200 Hz, $CDCl_3$) 9.95 (1H, d , $^4J_{HH}$ 1.7, C*H*O), 7.91 (1H, t, $^4J_{HH}$ 1.4, 2-H), 7.77 (1H, ddd, $^3J_{HF}$ 8.0, $^3J_{HH}$ 2.6, $^4J_{HH}$ 1.4, 6-H), 7.56 (1H, ddd, $^3J_{HF}$ 7.7, $^3J_{HH}$ 2.6, $^4J_{HH}$ 1.4, 4-H); δ_C (75 MHz, $CDCl_3$) 187.8 (d, $^4J_{CF}$ 1.9, CHO), 162.2 (d, $^1J_{CF}$ 253.8, 5-C), 138.2 (d, $^3J_{CF}$ 5.7, 1-C), 128.3 (d, $^4J_{CF}$ 3.6, 2-C), 123.8 (d, $^2J_{CF}$ 25.5, 4-C), 118.9 (d, $^2J_{CF}$ 22.4, 6-C'), 114.7 (d, $^4J_{CF}$ 2.9, CN), 114.1 (d, $^3J_{CF}$ 8.2, 3-C'); m/z (EI^+) 149.1 (M^+, C_8H_4FNO require 149.2), 131.6 (100), 105.3 (68).

3,5-Dinitrobenzyl-(3-cyano)-benzoate (51) (75%) as a white solid m.p. 218-220°C; ν_{max}(KBr)/cm^{-1}: 2260 (-CN), 1749.9 (C=O); 1527.4 (-NO_2); 1282.3; δ_H (300 MHz, $CDCl_3$) 8.75 (2H, m, 2'-H), 8.72 (1H, t, $^4J_{HH}$ 2.11, 4'-H), 8.35 (1H, t, $^3J_{HH}$ 1.74, 2-H), 8.26 (1H, dt, $^3J_{HH}$ 7.96, $^4J_{HH}$ 1.52, 6-H), 7.97 (1H, dt, $^3J_{HH}$ 7.63, $^4J_{HH}$ 1.61, 4-H), 7.69 (1H, t, $^3J_{HH}$ 8.34, 5-H), 5.63 (2H, s, CH_2); δ_c (125 MHz, $CDCl_3$) 163.6 (s, *C*=O), 148.0 (s, 3-C'), 139.9 (s, 1'-C), 136.4 (s, 4-C), 133.4 (s, 6-C), 132.6 (s, 2-C), 130.3 (s, 1-C), 129.9 (s, 5-C), 128.3 (s, 2-C'), 117.9 (s, 4-C'), 117.3 (s, CN), 112.1 (s, 3-C), 64.6 (s, CH_2); m/z (EI$^+$): 327.0 (M^+, $C_{15}H_9N_3O_6$ requires 327), 130(100), 102 (56); accurate mass: 327.0490 ($C_{15}H_9N_3O_6$ requires 327.0491).

The reaction was repeated using different solvents and the results are presented in table below.

Entry	Solvent	T (°C)	Crude product (conv. %)	Yield Ar-F (%)	Yield CFO (%)
1	CH_3CN	0	34	23	75
2	HCOOH	15	36	41	50

4. Fluorination of isophthalaldehyde (52)

Elemental fluorine (54 mmol, 3eq.) was passed through a solution of isophthalaldehyde (2.40 g, 18 mmol) in acetonitrile (150 ml). ^{19}F NMR of the reaction mixture showed the presence of 5-fluoroisophthalaldehyde **(54)** (35%): δ_F (200 MHz, $CDCl_3$) −109.4 (dt, $^3J_{FF}$ 20.1, $^3J_{HF}$ 6.8); and 3-formylbenzyl fluoride **(53)** (57 %); δ_F (200 MHz, $CDCl_3$) 20.3 (s); in the ratio 1: 1.6 in 16% conversion.

3,5-Dinitrobenzyl alcohol was added to the reaction mixture and stirred at room temperature. Pyridine (1 ml) was added and the reaction was stirred for two hours. The reaction mixture was poured into water, extracted by dichloromethane (3×100 ml), dried ($MgSO_4$) and evaporated to give a dark brown crude product. Purification by column chromatography gave:

5-fluoroisophthalaldehyde (54) (35%): δ_F (300 MHz, $CDCl_3$) −109.4 (dt, $^3J_{FF}$ 20.1, $^3J_{HF}$ 6.8); δ_H (300 MHz, $CDCl_3$) 10.04 (2H, m, *CHO*), 8.16 (1H, br.s, 3-H), 7.72 (1H d, $^3J_{HF}$

7.82, $^4J_{HH}$ 1.2, 6-H); m/z (EI^+) 151.0 (M^+, $C_8H_5FN_2O_2$ requires 330, 2%), 133 (100), 105 (86), 77 (88), 51 (58); (as compared to the literature data [136])

3.5 dinitrobenzyl-(3-formyl)-benzoate (55) (0.51 g, 57%) as a white solid: m.p.139.2-141.5°C. ν_{max}(KBr)/cm^{-1}: 2759.5, 1731.9 (C=O); 1521.4 (-NO_2); 1332.2; 1286.3; δ_H (300 MHz, $CDCl_3$) 10.00 (1H, s, C*H*O), 8.81 (1H, t, $^4J_{HH}$ 2.1, 4'-H), 8.73 (2H, dt, $^4J_{HH}$ 2.0, $^5J_{HH}$ 0.5, 2'-H, 6'-H), 8.45 (1H, dd, $^3J_{HH}$ 1.3, $^3J_{HH}$ 1.3, 2-H), 8.25 (1H, dd, $^3J_{HH}$ 7.7, $^4J_{HH}$ 1.3, 6-H), 8.09 (1H, dd, $^3J_{HH}$ 7.6, $^4J_{HH}$ 1.3, 4-H), 7.66 (1H, t, $^3J_{HH}$ 7.6, 5-H), 5.61 (2H, s, CH_2); δ_c (125 MHz, $CDCl_3$) 191.7 (s, CHO), 165.0 (s, *C*=O), 148.9 (s, 3'-C), 141.6 (s, 1'-C), 137.3 (s, 3-C), 135.0 (s, 6-C), 134.1 (s, 4-C), 130.8 (s, 1-C), 130.5 (s, 2-C), 128.7 (s, 2-C'), 128.1 (s, 5-C), 118.5 (s, 4-C'), 65.0 (s, *C*H_2); m/z (EI^+): 329.0 (5, $C_{15}H_{10}N_2O_7$ requires 330). 313.0 (24), 149 (42), 133 (100), 105.0 (64); accurate mass: Found: 330.0486, $C_{15}H_{10}N_2O_7$ requires 330.0485.

The reaction was repeated in different solvents and results are presented in table below.

Solvent	T (°C)	Crude product (conv. %)	Yield Ar-F (%)	Yield CFO (%)
CH_3CN	0	16	35	57
H_2SO_4	15	1	92	0

5. Fluorination of 3-trifluoromethylbenzaldehyde (56)

Elemental fluorine (24 mmol, 3 eq.) was passed through a solution of 3-trifluoromethylbenzaldehyde **(56)** (1.4 g, 8 mmol) in acetonitrile (150 ml). After completion of the reaction, pure nitrogen was purged through the reaction mixture for 15 minutes. ^{19}F NMR of the reaction mixture showed the presence of 5-fluoro-3-trifluoromethylbenzaldehyde **(57)** δ_F(200 MHz, $CDCl_3$) −110.7 (1F, t, $^3J_{FF}$ 8.9, 5-C-*F*); −63.4 (3F, s, CF_3); and 3-trifluoromethylbenzaldehyde fluoride **(58)** δ_F (200 MHz, $CDCl_3$) 11.3 (1F, s, CFO) −63.4 (3F, s, CF_3); in the ratio 1:1.8 in 38% conversion.

3,5-Dinitrobenzyl alcohol was added to the reaction mixture and stirred at room temperature. Pyridine (1 ml) was added and the reaction was stirred for two hours. The reaction mixture was poured to into water, extracted by dichloromethane (3×100 ml), dried ($MgSO_4$) and evaporated to give a dark brown crude product. Purification by column chromatography gave **5-fluoro-3-trifluoromethylbenzaldehyde (57)** (0.5 g. 35%) as a

colorless liquid δ_F (200 MHz, $CDCl_3$) −110.7 (1F, t, $^3J_{FF}$ 8.8, 5-C-*F*) −63.4 (3F, s, CF_3) δ_H (300 MHz, $CDCl_3$) 9.87 (1H, s, C*H*O), 7.77 (1H, m, 2-H), 7.54 (1H, dt, $^3J_{HF}$ 8.8, $^4J_{HH}$ 2.7, 6-H), 7.42 (1H, m, 4-H); δ_c (125 MHz, $CDCl_3$) 190.8 (d, $^4J_{CF}$ 1.9, *C*HO), 161.1 (dq, $^1J_{CF}$ 246.3, $^2J_{C\text{-}F}$ 23.8, C-F), 138.1 (d, $^3J_{CF}$ 6.1, 1-C), 133.1 (dq, $^3J_{CF}$ 8.14, $^2J_{CF}$ 17.1, 3-*C*), 122.7 (d, $^4J_{CF}$ 3.37, 2-C) 120.5 (d, $^2J_{CF}$ 22.4, 6-C), 118.8 (q, $^1J_{CF}$ 234.5, CF_3) 117.9 (dq, $^2J_{CF}$ 25.3, $^3J_{CF}$ 12.3, 4-C); m/z (EI^+) 192.2 (M^+, $C_8H_4F_4O$ requires 192.3), 191 (100), 190 (62), 173 (88),145 (78): (as authentic sample Aldrich Co.).

and **(3,5-dinitrobenzyl)-3-trifluoromethyl benzoate (59)** (0.68 g, 63%) as a white solid m.p. 149-151°C; (Found C, 48.3; H, 2.5; N, 7.3 $C_{15}H_9F_3N_2O_6$ requires C, 48.6; H, 2.4; N, 8.6 %); ν_{max}(KBr)/cm^{-1}: 2351.3; 1715.7 (C=O); 1538.4; 1342.9; 1275.3; δ_H (300MHz, $CDCl_3$) 8.97 (1H, br s, 4-H'), 8.67 (2H, d, $^3J_{HH}$ 1.3, 2-H', 6-H'), 8.31 (1H, s, 2-H), 8.27 (1H, d, $^3J_{HH}$ 7.1, 4-H), 7.85 (1H, d, $^3J_{HH}$ 8.4, 6-H), 7.65 (1H, d, $^3J_{HH}$ 9.1, 5-H), 5.75 (2H, s, CH_2), δ_c (125MHz, $CDCl_3$) 165.7 (s, *C*=O), 149.1 (s, 3-C'), 140.6 (s, 1-C'), 133.2 (s, 6-C), 131.3 (q, $^2J_{CF}$ 32.2, 3-C), 130.5 (q, $^3J_{CF}$ 3.39, 4-C), 130.0 (s, 1-C), 129.7 (s, 5-C), 129.3 (s, 2-C'), 126.9 (q, $^3J_{CF}$ 3.97, 2-C), 118.2 (q, $^1J_{CF}$ 273.2, CF_3) 118.0 (s, 4-C'), 64.6 (s, *C*H_2), m/z (EI^+) 370.1 (M^+, $C_{15}H_9F_3N_2O_6$ requires 370) 351.3 (100), 323 (38), 150 (42);

6. Fluorination of 4-trifluoromethylbenzaldehyde (60)

Elemental fluorine (24 mmol, 3 eq.) was passed through a solution of 4-trifluoromethyl-benzaldehyde **(60)** (1.4 g, 8 mmol) in acetonitrile (150 ml). ^{19}F NMR of the reaction mixture showed the presence of 5-fluoro-4-trifluoromethyl-benzaldehyde **(62)** δ_F (ppm) −115.6 (1F, dd, $^3J_{FF}$ 10.5, $^3J_{HF}$ 9.8), −64.3 (3F, s, CF_3); and 4-trifluoromethylbenzoyl fluoride **(61)** δ_F 21.3 (s), −64.3 (3F, s, CF_3); in the ratio 1: 1.96 in 38% conversion.

3,5-Dinitrobenzyl alcohol was added to the reaction mixture and stirred at room temperature. Pyridine (1 ml) was added and the reaction was stirred for two hours. The reaction mixture was poured into water, extracted by dichloromethane (3×100 ml), dried ($MgSO_4$) and evaporated to give a dark brown crude product. Purification by column chromatography gave **5-fluoro-trifluoromethylbenzaldehyde (62)** as a light yellow oil (0.87 g, 25%), δ_F (200 MHz, $CDCl_3$) −115.6 (dd, $^3J_{FF}$ 10.48, $^3J_{HF}$ 9.83), −64.3 (3F, s, CF_3); δ_H (200 Hz, $CDCl_3$) 10.2 (1H, s, CHO), 8.6 (1H, d, $^3J_{HF}$ 9.8, C-6), 8.3 (1H, dd, $^3J_{HH}$ 6.8,

$^5J_{HH}$ 1.8, C-3), 7.6 (1H, d, $^3J_{HH}$ 7.8, C-2), m/z (EI$^+$) 192.2 (M^+, $C_8H_4F_4O$ requires 192.3), 191 (100), 190 (62), 173 (88), 145 (78); (as literature data [101])

and **(3,5-dinitrobenzyl)-4-trifluoromethyl benzoate (64)** (1.8 g, 51%) as a white solid; mp. 149-151°C; (Found: C, 48.7; H, 2.4; N, 7.6. $C_{15}H_9F_3N_2O_6$ requires C, 48.6; H, 2.4; N, 7.6 %); ν_{max}(KBr)/cm^{-1}: 2345.3; 1715.5 (C=O); 1532.3; 1336.9; 1269.5; δ_H (300MHz, $CDCl_3$) 8.92 (1H, t, $^4J_{HH}$ 1.7, 2-H'), 8.86 (2H, t, $^3J_{HH}$ 1.3, 2-H'), 8.31 (1H, d, $^3J_{HH}$ 7.8, 2-H), 7.89 (2H, d, $^3J_{HH}$ 8.8, 3-H), 5.75 (2H, s, CH_2); δ_c (125MHz, $CDCl_3$) 164.7 (s, *C*=O), 148.8 (s, 3-C'), 140.6 (s, 1-C'), 135.3 (q, $^2J_{CF}$ 32.5, 4-C), 130.7 (s, 1-C), 130.4 (s, 2-C), 128.3 (s, 2-C'), 125.3 (q, $^3J_{CF}$ 3.75, 3-C), 118.7 (s, 4-C'), 118.2 (q, $^1J_{CF}$ 245.2, CF_3), 65.2 (s, CH_2); m/z (EI$^+$) 368.9 (M^+, $C_{15}H_9F_3N_2O_6$ requires 370), 330.3 (24), 180 (100), 150 (42); (as literature data[101])

7. Fluorination of 4-cyanobenzaldehyde (65)

Elemental fluorine (33 mmol, 3eq.) was passed through a solution of 4-cyanobenzaldehyde **(65)** (1.5 g, 11 mmol) in acetonitrile (150 ml). ^{19}F NMR of the reaction mixture showed the presence of 6-fluoro-4-cyanobenzaldehyde **(67)** δ_F (ppm) −119.6 (dd, $^3J_{HF}$ 9.48, $^3J_{HF}$ 7.81) and 4-cyanobenzoyl fluoride **(66)** δ_F (ppm) 20.3 (s) in the ratio 1:4.0 in 44% conversion.

3,5-Dinitrobenzyl alcohol was added to the reaction mixture and stirred at room temperature. Pyridine (1 ml) was added and the reaction was stirred for two hours. The reaction mixture was poured into water, extracted by dichloromethane (3×100 ml), dried ($MgSO_4$) and evaporated to give a dark brown crude product. Purification by column chromatography gave **6-fluoro-4-cyanobenzaldehyde (67)** (0.39 g, 17%) as a pale yellow solid m.p. 71-72°C; δ_F (200 MHz, $CDCl_3$) −119.6 (1F, dd, $^3J_{HF}$ 9.4, $^3J_{HF}$ 7.8); δ_H (400MHz, $CDCl_3$) 10.33 (1H, d, $^4J_{HH}$ 0.7 *CHO*), 7.92 (1H, dd, $^3J_{HH}$ 7.7, $^3J_{HF}$ 6.6 2-H), 7.51 (1H, dq, $^3J_{HH}$ 7.2, $^4J_{HF}$ 0.7, 3-H), 7.45 (1H, dd, $^3J_{HF}$ 9.4, $^3J_{HH}$ 1.7 5-H); δ_c(100MHz, $CDCl_3$) 182.5 (d, $^3J_{CF}$ 6.7 *C*HO), 162.5 (d, $^1J_{CF}$ 241.3, *C*-F), 128.9 (d, $^4J_{CF}$ 2.6, 3-*C*), 127.4 (d, $^3J_{CF}$ 4.2, 2-C), 127.1 (d, $^2J_{CF}$ 33.7, 1-C) 119.7 (d, $^2J_{CF}$ 24.3 5-C), 118.6 (d, $^3J_{CF}$ 9.9, 4-C), 115.5 (d, $^4J_{CF}$ 2.7, CN); m/z (EI$^+$) 150.0 (M^+, C_8H_4FNO requires 149.3), 130.4 (100), 101.9 (58). (as literature data [130]).

and **5-dinitrobenzyl-(4-cyano)-benzoate (70)** (2.2 g, 61%) as a white solid mp. 199.9-201.6°C (Found: C, 54.9; H, 2.7; N, 12.9. $C_{14}H_{10}N_2O_6$ requires C, 55.0; H, 2.7; N, 12.8%);

δ_H (300MHz, $CDCl_3$) 9.02 (1H, t, $^4J_{HH}$ 1.03, 4-H'), 8.50 (2H, t, $^3J_{HH}$ 1.22, 2-H'), 8.15 (1H, d, $^3J_{HH}$ 7.21, 2-H), 7.60 (2H, d, $^3J_{HH}$ 8.05, 3-H), 5.51 (2H, s, CH_2); δ_c (125MHz, $CDCl_3$) 168.7 (s, *C*=O), 148.8 (s, 3-C'), 142.3 (s, 1-C'), 134.7 (s, 1-C), 131.4 (s, 3-C), 130.0 (s, C-2), 128.3 (s, 2-C'), 117.4 (s, 4-C'), 116.7 (s, 4-C), 116.2 (s, CN), 69.2 (s, CH_2),; m/z (EI^+): 327.0 (M^+, $C_{15}H_9N_3O_6$ requires 327) 131(100), 92 (59);

8. Fluorination of 4-methylbenzaldehyde (71)

Elemental fluorine (37.5 mmol, 3 eq.) was passed through a solution of 4-methylbenzaldehyde (1.5 g, 12.5 mmol) in acetonitrile (150 ml). ^{19}F NMR of the reaction mixture showed the presence of 5-fluoro-4-methylbenzaldehyde (73 %) δ_F −116.5 (qt, $^3J_{HF}$ 10.16, $^5J_{HF}$ 2.07); and 5-fluoro-4-methylbenzaldehyde (7 %) δ_F −126.9 (t, $^3J_{HF}$ 6.77) in the ratio 7.3: 1 in 58% conversion. The reaction mixture was poured into water, extracted by dichloromethane (3×100 ml), dried ($MgSO_4$) and evaporated to give a dark brown crude product. Purification by column chromatography gave **5-fluoro-4-methylbenzaldehyde (72)** (0.67 g. 73%) as a bright yellow liquid; (Found: C 69.3; H, 5.4. C_8H_8FO requires C, 69.5; H, 5.1 %); δ_F (200 Hz, $CDCl_3$) −116.5 (qt, $^3J_{HF}$ 9.4, $^5J_{HF}$ 2.0); δ_H (400MHz, $CDCl_3$) 9.87 (1H, d, $^5J_{HF}$ 1.8, C*H*O), 7.45 (1H, dd, $^3J_{HH}$ 8.0, $^5J_{HH}$ 1.5, 2-H), 7.36 (1H, dd, $^3J_{HH}$ 9.4, $^5J_{HH}$ 1.5, 6-H), 7.21 (1H, t, $^3J_{HH}$ 8.0, 3-H), 2.23 (d, $^5J_{HF}$ 1.9, CH_3); δ_c(100MHz, $CDCl_3$) 191.0 (d, $^4J_{CF}$ 2.0, *C*HO), 160.6 (d, $^1J_{CF}$ 246.3, *C*-F), 136.2 (d, $^4J_{CF}$ 5.2, 4-*C*), 132.2 (d, $^2J_{CF}$ 18.8, 1-C), 132.3 (d, $^4J_{CF}$ 4.8, 6-C) 126.1 (d, $^2J_{CF}$ 3.0 5-C), 122.5 (d, $^2J_{CF}$ 22.9, 3-C), 14.5 (d, $^3J_{CF}$ 3.5, CH_3); m/z (EI^+) 139.0 (M^+, C_8H_4FO requires 138.3, 7),138.1 (100) 137.0 (88), 113.0 (98); (as literature data [130]).

9. Fluorination of 4-methoxy-benzaldehyde (72)

Elemental fluorine (44 mmol, 3 eq.) was passed through a solution of the 4-methoxy-benzaldehyde (2 g, 14.7 mmol) in acetonitrile (150 ml). ^{19}F NMR of the reaction mixture showed the presence of 5-fluoro-4-methoxybenzaldehyde **(73)** (79%); δ_F (200 Hz, $CDCl_3$) −133.9 (dd, $^3J_{HF}$ 10.2, $^3J_{HF}$ 7.8); and 3,5-difluoro-4-methoxybenzaldehyde **(74)** (12%) δ_F (200 Hz, $CDCl_3$) −126.9 (dt, $^3J_{HF}$ 6.8, $^5J_{FF}$ 2.8) in the ratio 1: 0.4 in 66% conversion.

The reaction mixture was poured into water, extracted by dichloromethane (3×100 ml), dried ($MgSO_4$) and evaporated to give a dark brown crude product. Purification by column chromatography gave **5-fluoro-4-methoxybenzaldehyde (73)** as a brown liquid (1.07 g. 79%); δ_F (200 MHz, $CDCl_3$) −133.9 (1F, dd, $^3J_{HF}$ 7.9); δ_H (400 MHz, $CDCl_3$) 9.77 (1H, d, $^5J_{HF}$ 1.9, C*H*O), 7.51 (2H, m, 2-H, 6-H), 7.01 (1H, t, $^3J_{HF}$ 7.9, 3-H), 3.89 (t, $^5J_{HF}$ 1.4, OC*H*$_3$); δ_c(100MHz, $CDCl_3$) 190.0 (d, $^4J_{CF}$ 2.13, *C*HO), 152.6 (d, $^1J_{CF}$ 248.3, *C*-F), 153.29 (d, $^2J_{CF}$ 11.01, 4-*C*), 130.3 (d, $^3J_{CF}$ 4.8, 1-C), 128.3 (d, $^2J_{CF}$ 3.37, 2-C) 115.7 (d, $^2J_{CF}$ 24.3 6-C), 118.6 (d, $^3J_{CF}$ 7.9, 3-C), 56.5 (s, CH_3); m/z (EI^+) 156.0 (M^+, C_8H_4FNO requires 154.3, 2), 154.0 (88), 153.0 (98); (as literature data [123])

and a yellow liquid **3,5-difluoro-4-methoxybenzaldehyde (74)** (0.18 g, 12%): −126.9 (dt, $^3J_{HF}$ 6.77, $^5J_{FF}$ 2.77), δ_H (300 MHz, $CDCl_3$) 9.76 (1H, t, $^5J_{HF}$ 1.80, C*H*O) 7.39 (2H, $^3J_{HF}$ 7.80 C-2, C-6), 4.07 (t, $^5J_{HF}$ 1.80, OC*H*$_3$); δ_c (125MHz, $CDCl_3$) 188.2 (s, *C*=O), 156.2 (dd, $^1J_{CF}$ 252.1 $^3J_{CF}$ 5.96 3-C, 5-C), 141.5 (t, $^2J_{CF}$ 13.5, 4-C), 129.1 (m, 1-C), 112.1 (m, 2-C), 60.7 (s, OCH_3); m/z (EI^+): 174.1 (M^+, $C_8H_6F_2O_2$ requires 172.1, 2) 172 (84), 171 (100); (as literature data [123])

8.2 Fluorination of benzaldehyde derivatives using Selectfluor™

1. Fluorination of isophthalobenzaldehyde (52)

A mixture isophthalobenzaldehyde **(52)** (0.7 g, 5.34 mmol) and Selectfluor™ (2.08 g. 5.88 mmol) were refluxed in acetonitrile (150 ml). After 25 h, the ^{19}F NMR spectrum of the reaction mixture showed the presence of 3-formylbenzoyl fluoride **(53)** (78%); δ_F (ppm) 20.3 (s); in conversion (84%). 3,5-Dinitrobenzyl alcohol was added to the reaction mixture and stirred at reflux temperature. Pyridine (1 ml) was added and the reaction was stirred for ten hours until competition. The reaction mixture was poured to into water, extracted by dichloromethane (3×100 ml), dried ($MgSO_4$) and evaporated to give a dark brown crude product. Purification by recrystalisaton in DCM gave pure 3,5-dinitrobenzyl-(3-formyl)-benzoate **(55)** (1.05 g) as a white solid;(Spectral data as above).

2. Fluorination of 3-formylbenzonitrile (48)

3-Formylbenzonitrile **(48)** (0.7 g, 5.46 mmol) and Selectfluor™ (2.13 g. 6.1 mmol) were refluxed in acetonitrile (150 ml). After 25 h, the ^{19}F NMR spectrum of the reaction mixture showed the presence of 3-formylbenzoyl fluoride **(49)** (93%); δ_F (200 Hz, $CDCl_3$) 20.3 (s); in conversion (78%). 3,5-Dinitrobenzyl alcohol was added to the reaction mixture and stirred at reflux temperature. Pyridine (1 ml) was added and the reaction was stirred for ten hours until competition. The reaction mixture was poured into water, extracted by dichloromethane (3×100 ml), dried ($MgSO_4$) and evaporated to give a dark brown crude product. Purification by recrystalisaton in DCM gave pure 3,5-dinitrobenzyl-(3-cyano)-benzoate **(50)** (1.15 g) as a white solid; (Spectral data as above).

3. Fluorination of 3-nitrobenzaldehyde (44)

3-Nitrobenzladehyde **(44)** (0.8 g, 5.29 mmol) and Selectfluor™ (2.13 g. 5.83 mmol) were refluxed in acetonitrile (150 ml). After 25 h, the ^{19}F NMR spectrum of the reaction mixture showed the presence of 3-nitrobenzoyl fluoride (89%) δ_F (ppm) 19.3 (s) in conversion (69%). 3,5-Dinitrobenzyl alcohol was added to the reaction mixture and stirred at reflux temperature. Pyridine (1 ml) was added and the reaction was stirred for ten hours until competition. The reaction mixture was poured into water, extracted by dichloromethane (3×100 ml), dried ($MgSO_4$) and evaporated to give a dark brown crude product. Purification by recrystalisaton in DCM gave pure 3,5-dinitrobenzyl-(3-nitro)-benzoate **(47)** (1.80 g) as a yellow solid.(Spectral data as above)

4. Fluorination of 4-trifluoromethylbenzaldehyde (60)

4-Trifluoromethylbenzaldehyde **(56)** (0.9 g, 5.19 mmol) and Selectfluor™ (2.13 g. 5.83 mmol) were refluxed in acetonitrile (150 ml). After 25 h, the ^{19}F NMR spectrum of the reaction mixture showed the presence of 4-trifluoromethylbenzoyl fluoride **(61)** (76%) δ_F (200 Hz, $CDCl_3$) 19.3 (s) in conversion (87%). 3,5-Dinitrophenylmethanol was added to the reaction mixture and stirred at reflux temperature. Pyridine (1 ml) was added and the reaction was stirred for ten hours until competition. The reaction mixture was poured into water, extracted by dichloromethane (3×100 ml), dried ($MgSO_4$) and evaporated to give a

dark brown crude product. Purification by recrystalisaton in DCM gave a pure 3,5-dinitrobenzyl-(4-trifluoromethyl)-benzoate **(64)** (1.92 g) as a yellow solid. (Spectral data as above).

5. Fluorination of 4-methoxybenzaldehyde (72)

4-Metoxybenzaldehyde **(74)** (0.85 g, 5.19 mmol) and Selectfluor™ (2.13 g. 5.71 mmol) were refluxed in acetonitrile (150 ml). After 25 h, the ^{19}F NMR spectrum of the reaction mixture showed the presence of 5-fluoro-4-methoxybenzaldehyde **(73)** (68 %) δ_F (200 Hz, $CDCl_3$) −133.8 (t, $^3J_{HF}$ 10.16, $^3J_{HF}$ 7.81) and 3,5-difluoro-4-methoxy-benzaldehyde **(74)** (11%) δ_F(200 Hz, $CDCl_3$) −126.9 (dt, $^3J_{HF}$ 6.77) in ratio 6.1:1 and conversion (51%). The reaction mixture was poured into water, extracted by dichloromethane (3×100 ml), dried ($MgSO_4$) and evaporated to give a dark brown crude product. Purification by column chromatography using eluent hexane: DCM 15:1 gave a pure 5-fluoro-4-methoxybenzaldehyde **(73)** (0.36 g) as a yellow oil and 3,5-difluoro-4-methoxy-benzaldehyde **(74)** (0.07 g) as a brown oil; (Spectral data as above).

Chapter 9 Experimental to Chapter 5

9.1 Experiments in microreactor (general procedure)

A cryostat that cools the microreactor was set up at -15°C for at least for a 4 h to cool the microreactor to 2-3°C. The compound was dissolved in acetonitrile or other solvent (100 ml). The solution (60 ml) of substrate was slowly injected using a syringe to fill the substrate chamber. The flow of the substrate (0.1- 4 $mlh^{-1}ch^{-1}$) through the microreactor was controlled by a syringe drive. The elemental fluorine (56 – 100 $mlmin^{-1}$, 10% F_2/N_2) was introduced to the solution containing substrate (40 ml), while the rest of the solution remained in the reactor chamber. After the reaction was competed, nitrogen was passed through the system. A standard aqueous work up was applied to the collected reaction mixture to give the crude product. The conversion was determined according to the ^{19}F NMR or ^{1}H NMR.

9.2 A procedure for the operation of Microreactor Rig

The microreactor is connected to the "to microreactor" and "from microreactor" ports and to the substrate supply by PTFE tubes. The substrate flow is controlled by syringe Pump drive.

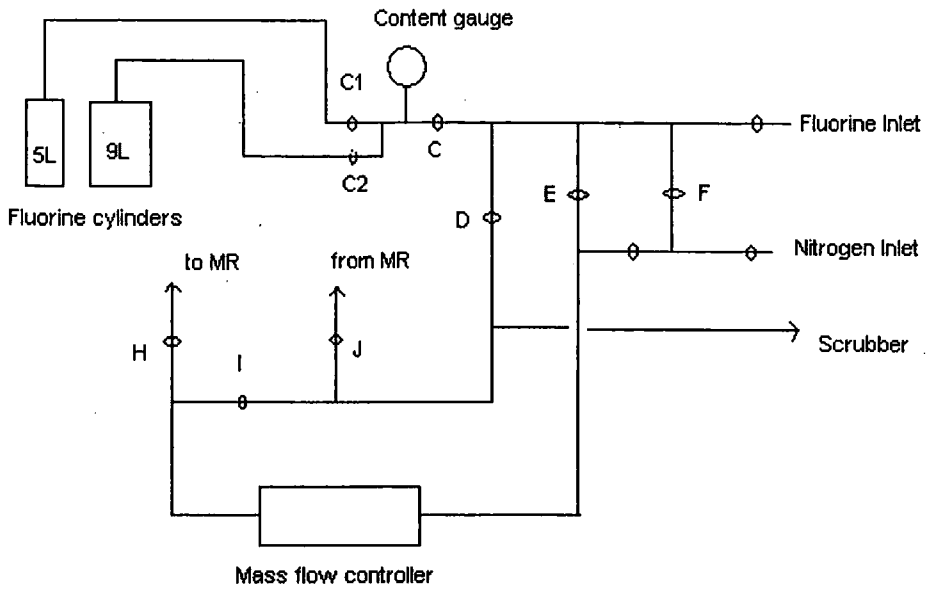


Figure 5.3

1) Ensure that all valves are closed
2) Open valves A, G, H, and I
3) Set flow to desired level and purge with nitrogen for 20min
4) Close valves A and G
5) Open valves C1, C2, C and than valve E (fluorine flow is automatically regulated using flow controller Brooks 5850S)
6) Start substrate flow 5 minutes after fluorine flow
7) Termination of the experiment involves closing valves C1, C2, C and than E
8) Stop substrate flow and withdraw 30 ml of substrate with syringe from reservoir
9) Open valves A and G and purge for 15 min
10) Close all valves

The microreactor was cleaned by syringing the remaining substrate from the MR reservoir and than flushing through acetonitrile or formic acid (2×200 ml). The reservoirs and channels of microreactor were then dried by passing nitrogen through at 10 ml/min for several hours. If some insoluble particles are blocking the channels, it is necessary to open the microreactor and mechanically remove the blockage.

9.3 Benzaldehyde derivatives

1. 4-trifluoromethyl-benzaldehyde (56)

(1) Elemental fluorine (3eq., 9.8 ml h^{-1} ch^{-1}) and solution of 4-trifluoromethylbenzaldehyde **(56)** (4 ml h^{-1} ch^{-1}, 4.50 g, 8.7 mmol) in acetonitrile (100 ml) was passed through MR. After 66.6min. of the reaction, the collected reaction mixture was poured into the water and extracted by dichloromethane (3×100 ml), dried ($MgSO_4$) and evaporated to give the crude product (conv. 12%) contains two products 5-fluoro-4-trifluoromethyl-benzaldehyde **(57)** (32%) and 4-trifluoromethyl-benzoyl fluoride **(58)** (59%).

(2) Elemental fluorine (3eq. 8.7 ml h^{-1} ch^{-1}) and solution of 4-trifluoromethylbenzaldehyde **(56)** (2 ml h^{-1} ch^{-1}, 8 g, 38.8 mmol) in acetonitrile (100 ml) was passed through MR. After 133min. of the reaction, the collected reaction mixture was poured into the water and extracted by dichloromethane (3×100 ml), dried ($MgSO_4$) and evaporated to give the crude product (conv. 57%) contains two products 5-fluoro-4-trifluoromethyl-benzaldehyde **(57)** (31%) and 4-trifluoromethylbenzoyl fluoride **(58)** (64 %).

2. 3-nitrobenzaldehyde (44)

Elemental fluorine (3eq. 7.03 ml h^{-1} ch^{-1}) and solution of 3-nitrobenzaldehyde **(44)** (2 ml h^{-1} ch^{-1}) in acetonitrile (100 ml) was passed through MR. After 133 min. of the reaction, the collected reaction mixture was poured into the water and extracted by dichloromethane (3×100 ml), dried ($MgSO_4$) and evaporated to give the crude product (conv. 52%) which contains two products 5-fluoro-3-nitrobenzaldehyde **(45)** (16%) and 3-nitrobenzoyl fluoride **(46)** (76%).

3. 3-formyl-benzonitrile (48)

Elemental fluorine (3eq. 8.55 ml $h^{-1}ch^{-1}$) and solution of 3-formyl-benzonitrile **(48)** (2 ml h^{-1} ch^{-1}, 5.0 g, 38.1 mmol) in acetonitrile (100 ml) was passed through MR. After 133 min. of the reaction, the collected reaction mixture was poured into the water and extracted by dichloromethane (3×100 ml), dried ($MgSO_4$) and evaporated to give the crude product (conv. 48%) contains two products 5-fluoro-3-formyl-benzonitrile **(50)** (22%) and 3-cyano-benzoyl fluoride **(49)** (74%).

4. 3-isophthalaldehyde (52)

(3) Elemental fluorine (3eq. 8.22 ml h^{-1} ch^{-1}) and solution of 3-isophthalaldehyde **(52)** (2 ml h^{-1} ch^{-1}, 5.0 g, 37 mmol) in acetonitrile (100 ml) was passed through MR. After 133 min. of the reaction, the collected reaction mixture was poured into the water and extracted by dichloromethane (3×100 ml), dried ($MgSO_4$) and evaporated to give the crude product (conv. 46%) contains two products 5-fluoro-3-isophthalaldehyde **(54)** (23%) and 3-formyl-benzoyl fluoride **(54)** (65%).

9.4 Nitrobenzene derivatives

1. 3-Nitro-benzonitrile (33)

Elemental fluorine (60 ml h^{-1} min^{-1}, 1.78 mmol h^{-1} ch^{-1}) and solution of 3-nitrobenzonitrile **(33)** in acetonitrile (0.5 ml h^{-1} ch^{-1}, 0.42 mmol min^{-1} ch^{-1}) was passed through MR cooled at 2°C. After 240 min. of the reaction, the collected reaction mixture was poured into the water and extracted by dichloromethane (3×100 ml), dried ($MgSO_4$) and evaporated to give a dark orange crude product (1.92 g). Conversion determined to be 18% of which is 5-fluoro-3-nitrobenzonitrile **(34)** (95%).

3. 1,3-Dinitro-benzene (31)

(1) Elemental fluorine (4eq. 60 $mlmin^{-1}$, 1.78 mmol h^{-1} ch^{-1}) and solution of 1,3-dinitro-benzene **(31)** in acetonitrile (0.5 ml h^{-1} ch^{-1}, 0.45 mmol h^{-1} ch^{-1}) was passed through MR at 2°C. After 240 min. of the reaction, the collected reaction mixture was poured into the water and extracted by dichloromethane (3×100 ml), dried ($MgSO_4$) and evaporated to give a dark orange crude product (1.73 g). Conversion determined to be 18% of which is 5-fluoro-1,3-dinitro-benzene **(32)** (95%).

(2) Elemental fluorine (4eq. 60 ml min^{-1}, 1.78 mmol h^{-1} ch^{-1}) and solution of 1,3-dinitro-benzene in formic acid **(31)** (0.1 ml h^{-1} ch^{-1}, 0.45 mmol h^{-1} ch^{-1}) was passed through MR, cooled at 2°C. After 240 min. of the reaction, the collected reaction mixture was poured into the water and extracted by dichloromethane (3×100 ml), dried ($MgSO_4$) and

evaporated to give a dark orange crude product (1.92 g). Conversion determined to be 19% of which is 5-fluoro-1,3-dinitro-benzene **(32)** (96%).

(3) Elemental fluorine (12eq. 60 ml min^{-1}, 1.78 mmol h^{-1} ch^{-1}) and solution in 1,3-dinitro-benzene **(31)** (0.5 ml h^{-1} ch^{-1}, 0.14 $mmolmin^{-1}ch^{-1}$) in acetonitrile (80 ml) was passed through MR cooled at 2°C. After 240 min. of reaction, the collected reaction mixture was poured into the water and extracted by dichloromethane (3×100 ml), dried ($MgSO_4$) and evaporated to give a dark orange crude product (1.82 g). Conversion determined to be 27% of which is 5-fluoro-1,3-dinitro-benzene **(32)** (95%).

1. 2,4-Dinitrotoluene (18)

(1) Elemental fluorine (90 ml min^{-1}, 2.6 mmol min^{-1} ch^{-1}) and solution of 2,4-dinitrotoluene **(18)** (2 ml h^{-1} ch^{-1}, 0.87 mmol min^{-1} ch^{-1}) in acetonitrile (100 ml) were passed through MR cooled at 6°C. After 122 min. of the reaction, the collected reaction mixture was poured into the water and extracted by dichloromethane (3×100 ml), dried ($MgSO_4$) and evaporated to give a dark orange crude product (3.1 g). Conversion was determined to be 38% and the only products was 6-fluoro-2,4-dinitrotoluene **(19)** (98%).

(2) Elemental fluorine (12eq. 57 ml min^{-1}, 1.7 mmol h^{-1} ch^{-1}) and solution of 2,4-dinitrotoluene **(18)** (0.1 ml h^{-1} ch^{-1}, 0.14 mmol h^{-1} ch^{-1}) in acetonitrile (80 ml) were passed through MR cooled at 2°C. After 240 min. of the reaction, the collected reaction mixture was poured into the water and extracted by dichloromethane (3×100 ml), dried ($MgSO_4$) and evaporated to give a dark orange crude product (1.1 g). Conversion determined to be 99% of which is 6-fluoro-2,4-dinitrotoluene **(19)** (53 %).

5-fluoro-2,4-dinitrotoluene (77) (18%) δ_F (300 Hz, $CDCl_3$): −101.3 (d, $^3J_{HF}$ 7.9) δ_H (200 Hz, $CDCl_3$): 8.63 (1H, d, $^4J_{HF}$ 2.8, H-3), 7.29 (1H, d, $^3J_{HF}$ 8.1, H-6), 2.32 (3H, s CH_3), **m/z (EI$^+$)** 200 (M^+, $C_7H_5FN_2O_4$ requires 200.0, 21.9), 183 (95), 107 (82). (as compared to the literature data [155]),

1-Fluoromethyl-2,4-dinitro-benzene (78) (23%) δ_F (300 Hz, $CDCl_3$): −215.3 (t, $^2J_{HF}$ 45.8) δ_H (200 Hz, $CDCl_3$): 9.01 (1H, s, H-3), 8.42 (1H, d, $^3J_{HH}$ 6.1, H-5), 7.58 (1H, d, $^3J_{HH}$ 6.9, H-6) 5.35 (3H, d, $^2J_{HF}$ 42.9, CH_3), **m/z (EI$^+$)** 200.1 (M^+, $C_7H_5FN_2O_4$ requires 200.0, 11), 167 (92), 121 (82). (as literature data [155])

Appendix

Table 1. Crystal data and structure refinement for 5fluoro-3-nitrobenzaldehyde.

Identification code	04srv269	
Empirical formula	C7 H4 F N O3	
Formula weight	169.11	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 2(1)	
Unit cell dimensions	a = 3.7073(3) Å	α= 90°.
	b = 7.3982(6) Å	β= 96.0740(10)°.
	c = 12.4603(9) Å	γ = 90°.
Volume	339.83(5) $Å^3$	
Z	2	
Density (calculated)	1.653 Mg/m^3	
Absorption coefficient	0.148 mm^{-1}	
F(000)	172	
Crystal size	0.94 x 0.42 x 0.03 mm^3	
Theta range for data collection	1.64 to 30.50°.	
Index ranges	-5<=h<=5, -10<=k<=10, -17<=l<=17	
Reflections collected	4427	
Independent reflections	2044 [R(int) = 0.0145]	
Completeness to theta = 30.50°	99.0 %	
Absorption correction	None	
Max. and min. transmission	0.9956 and 0.8734	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2044 / 1 / 125	
Goodness-of-fit on F^2	1.141	
Final R indices [I>2sigma(I)]	R1 = 0.0342, wR2 = 0.0907	
R indices (all data)	R1 = 0.0358, wR2 = 0.1001	
Absolute structure parameter	0.6(6)	
Largest diff. peak and hole	0.468 and -0.219 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 04srv269. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	1586(3)	4897(1)	2527(1)	17(1)
C(2)	1688(3)	4074(1)	3524(1)	18(1)
F(2)	580(2)	5018(1)	4353(1)	28(1)
C(3)	2827(3)	2303(2)	3714(1)	18(1)
C(4)	3945(3)	1369(1)	2839(1)	16(1)
N(4)	5131(3)	-518(1)	2995(1)	21(1)
O(41)	4443(3)	-1293(1)	3815(1)	32(1)
O(42)	6721(3)	-1216(1)	2285(1)	30(1)
C(5)	3962(3)	2129(1)	1825(1)	16(1)
C(6)	2747(3)	3897(1)	1677(1)	16(1)
C(7)	2686(3)	4713(2)	587(1)	22(1)
O(7)	1500(3)	6201(2)	361(1)	32(1)

Table 3. Bond lengths [Å] and angles [57] for 04srv269.

C(1)-C(2)	1.3798(15)	C(4)-N(4)	1.4707(14)
C(1)-C(6)	1.3968(14)	N(4)-O(41)	1.2213(14)
C(1)-H(1)	0.92(2)	N(4)-O(42)	1.2269(13)
C(2)-F(2)	1.3469(11)	C(5)-C(6)	1.3895(14)
C(2)-C(3)	1.3892(15)	C(5)-H(5)	0.88(2)
C(3)-C(4)	1.3907(13)	C(6)-C(7)	1.4847(14)
C(3)-H(3)	0.92(2)	C(7)-O(7)	1.2079(16)
C(4)-C(5)	1.3836(14)	C(7)-H(7)	0.987(14)

C(2)-C(1)-C(6)	117.82(9)
C(2)-C(1)-H(1)	116.8(12)
C(6)-C(1)-H(1)	125.3(12)
F(2)-C(2)-C(1)	118.65(9)
F(2)-C(2)-C(3)	118.02(9)
C(1)-C(2)-C(3)	123.32(9)
C(2)-C(3)-C(4)	116.41(9)
C(2)-C(3)-H(3)	118.9(13)
C(4)-C(3)-H(3)	124.7(13)
C(5)-C(4)-C(3)	123.03(9)
C(5)-C(4)-N(4)	118.43(9)
C(3)-C(4)-N(4)	118.54(9)
O(41)-N(4)-O(42)	124.35(11)
O(41)-N(4)-C(4)	118.01(10)
O(42)-N(4)-C(4)	117.64(10)
C(4)-C(5)-C(6)	118.06(9)
C(4)-C(5)-H(5)	118.1(14)
C(6)-C(5)-H(5)	123.3(14)
C(5)-C(6)-C(1)	121.35(9)
C(5)-C(6)-C(7)	118.49(9)
C(1)-C(6)-C(7)	120.16(10)
O(7)-C(7)-C(6)	123.65(11)
O(7)-C(7)-H(7)	118.1(9)
C(6)-C(7)-H(7)	117.7(9)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 04srv269. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	16(1)	14(1)	22(1)	-1(1)	2(1)	1(1)
C(2)	18(1)	19(1)	18(1)	-5(1)	4(1)	0(1)
F(2)	35(1)	29(1)	22(1)	-8(1)	9(1)	7(1)
C(3)	18(1)	19(1)	16(1)	0(1)	3(1)	-2(1)
C(4)	16(1)	12(1)	19(1)	0(1)	1(1)	1(1)
N(4)	22(1)	14(1)	26(1)	-1(1)	-4(1)	2(1)
O(41)	48(1)	20(1)	28(1)	7(1)	-2(1)	1(1)
O(42)	34(1)	19(1)	38(1)	-2(1)	7(1)	8(1)
C(5)	15(1)	16(1)	16(1)	-2(1)	3(1)	1(1)
C(6)	14(1)	16(1)	17(1)	1(1)	2(1)	-1(1)
C(7)	23(1)	25(1)	19(1)	5(1)	3(1)	-1(1)
O(7)	38(1)	29(1)	29(1)	11(1)	3(1)	6(1)

Table 5. Hydrogen coordinates ($x\ 10^4$) and isotropic displacement parameters ($Å^2 x\ 10^3$) for 04srv269.

	x	y	z	U(eq)
H(1)	620(50)	6040(30)	2469(16)	36(5)
H(3)	2820(50)	1830(30)	4398(15)	29(5)
H(5)	4460(50)	1420(30)	1292(16)	32(5)
H(7)	3970(40)	4070(20)	48(13)	11(3)

Table 6. Torsion angles [57] for 04srv269.

C(6)-C(1)-C(2)-F(2)	179.98(9)
C(6)-C(1)-C(2)-C(3)	-1.01(16)
F(2)-C(2)-C(3)-C(4)	179.89(9)
C(1)-C(2)-C(3)-C(4)	0.87(15)
C(2)-C(3)-C(4)-C(5)	0.19(15)
C(2)-C(3)-C(4)-N(4)	-179.19(9)
C(5)-C(4)-N(4)-O(41)	-165.66(10)
C(3)-C(4)-N(4)-O(41)	13.75(14)
C(5)-C(4)-N(4)-O(42)	13.67(15)
C(3)-C(4)-N(4)-O(42)	-166.93(10)
C(3)-C(4)-C(5)-C(6)	-1.04(16)
N(4)-C(4)-C(5)-C(6)	178.34(9)
C(4)-C(5)-C(6)-C(1)	0.89(15)
C(4)-C(5)-C(6)-C(7)	-178.84(9)
C(2)-C(1)-C(6)-C(5)	0.09(15)
C(2)-C(1)-C(6)-C(7)	179.81(9)
C(5)-C(6)-C(7)-O(7)	175.86(11)
C(1)-C(6)-C(7)-O(7)	-3.87(17)

:

Table 7. Hydrogen bonds for 04srv269 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(3)-H(3)...F(2)#1	0.92(2)	2.50(2)	3.3013(13)	146.2(15)
C(1)-H(1)...O(42)#2	0.92(2)	2.49(2)	3.3908(14)	167.6(17)

Symmetry transformations used to generate equivalent atoms:

#1 -x,y-1/2,-z+1 #2 x-1,y+1,z

Table 1. Crystal data and structure refinement for 2,4dinitroacetanilide.

Identification code	jt68 block	
Empirical formula	C8 H7 N3 O5	
Formula weight	225.17	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$ (No. 14)	
Unit cell dimensions	a = 6.0813(3) Å	α= 90°
	b = 15.7150(8) Å	β= 92.018(3)°
	c = 9.7811(5) Å	γ = 90°
Volume	934.18(8) Å^3	
Z	4	
Density (calculated)	1.601 g/cm^3	
Absorption coefficient	0.136 mm^{-1}	
F(000)	464	
Crystal size	0.36 × 0.17 × 0.17 mm^3	
θ range for data collection	2.4 to 30.0°.	
Index ranges	$-8 \leq h \leq 8$, $-22 \leq k \leq 22$, $-13 \leq l \leq 13$	
Reflections collected	12749	
Independent reflections	2728 [R(int) = 0.0240]	
Reflections with I>2σ(I)	2378	
Completeness to θ = 30.0°	100.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2728 / 0 / 173	
Largest final shift/e.s.d. ratio	0.001	
Goodness-of-fit on F^2	1.057	
Final R indices [I>2σ(I)]	R1 = 0.0376, wR2 = 0.1093	
R indices (all data)	R1 = 0.0417, wR2 = 0.1123	
Largest diff. peak and hole	0.404 and -0.238 e.Å^{-3}	

Table 2. Atomic coordinates ($\times 10^5$) and equivalent isotropic displacement parameters ($Å^2 \times 10^4$) for 03srv055. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	2452(11)	4155(5)	69355(7)	262(2)
O(2)	69627(12)	20738(5)	78917(7)	272(2)
O(3)	92336(13)	24254(5)	63480(8)	327(2)
O(4)	86656(12)	16030(5)	18073(8)	308(2)
O(5)	60704(12)	7598(5)	10555(7)	282(2)
N(1)	34011(13)	12061(5)	72036(8)	209(2)
N(2)	75588(13)	20666(5)	66975(9)	216(2)
N(3)	69864(13)	11878(5)	19604(8)	217(2)
C(1)	42155(14)	12145(6)	58992(9)	181(2)
C(2)	62480(14)	16132(6)	56422(9)	183(2)
C(3)	71500(15)	15994(6)	43590(10)	192(2)
C(4)	60092(15)	11972(6)	33068(9)	187(2)
C(5)	39771(15)	8193(6)	34899(9)	196(2)
C(6)	30959(15)	8300(6)	47740(9)	195(2)
C(7)	14973(15)	8351(6)	76595(9)	204(2)
C(8)	11257(19)	10124(7)	91406(10)	257(2)

Table 3. Bond lengths [Å] and angles [57] for 03srv055.

O(1)-C(7)	1.2157(12)	C(1)-C(2)	1.4161(12)
O(2)-N(2)	1.2351(11)	C(2)-C(3)	1.3876(13)
O(3)-N(2)	1.2234(11)	C(3)-C(4)	1.3747(13)
O(4)-N(3)	1.2254(11)	C(3)-H(3)	0.937(14)
O(5)-N(3)	1.2294(11)	C(4)-C(5)	1.3884(12)
N(1)-C(7)	1.3840(12)	C(5)-C(6)	1.3829(13)
N(1)-C(1)	1.3849(12)	C(5)-H(5)	0.971(13)
N(1)-H(1)	0.904(15)	C(6)-H(6)	0.945(14)
H(1)...O(2)	1.875(15)	C(7)-C(8)	1.5001(13)
N(1)...O(2)	2.627(1)	C(8)-H(81)	0.939(18)
N(2)-C(2)	1.4665(12)	C(8)-H(82)	0.939(18)
N(3)-C(4)	1.4638(12)	C(8)-H(83)	0.956(17)
C(1)-C(6)	1.4096(12)		

C(7)-N(1)-C(1)	129.14(8)	C(5)-C(4)-N(3)	120.21(8)
C(7)-N(1)-H(1)	118.2(9)	C(6)-C(5)-C(4)	119.15(8)
C(1)-N(1)-H(1)	112.7(9)	C(6)-C(5)-H(5)	120.1(8)
O(3)-N(2)-O(2)	122.34(8)	C(4)-C(5)-H(5)	120.7(8)
O(3)-N(2)-C(2)	117.68(8)	C(5)-C(6)-C(1)	121.49(8)
O(2)-N(2)-C(2)	119.98(8)	C(5)-C(6)-H(6)	118.0(8)
O(4)-N(3)-O(5)	124.17(8)	C(1)-C(6)-H(6)	120.5(8)
O(4)-N(3)-C(4)	118.10(8)	O(1)-C(7)-N(1)	123.69(8)
O(5)-N(3)-C(4)	117.73(8)	O(1)-C(7)-C(8)	123.41(9)
N(1)-C(1)-C(6)	122.45(8)	N(1)-C(7)-C(8)	112.89(8)
N(1)-C(1)-C(2)	120.69(8)	C(7)-C(8)-H(81)	111.3(11)
C(6)-C(1)-C(2)	116.85(8)	C(7)-C(8)-H(82)	110.3(11)
C(3)-C(2)-C(1)	121.94(8)	H(81)-C(8)-H(82)	112.8(15)
C(3)-C(2)-N(2)	114.95(8)	C(7)-C(8)-H(83)	109.3(10)
C(1)-C(2)-N(2)	123.11(8)	H(81)-C(8)-H(83)	106.4(14)
C(4)-C(3)-C(2)	118.63(8)	H(82)-C(8)-H(83)	106.4(14)
C(4)-C(3)-H(3)	123.4(8)		
C(2)-C(3)-H(3)	117.9(8)		
C(3)-C(4)-C(5)	121.88(8)		
C(3)-C(4)-N(3)	117.90(8)		

N(1)-H(1)...O(2) 139.3(12)

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^4$) for 03srv055. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U_{11} + ... + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	242(3)	282(4)	264(4)	-40(3)	22(3)	-75(3)
O(2)	265(4)	314(4)	234(4)	-52(3)	-32(3)	-31(3)
O(3)	274(4)	339(4)	366(4)	-62(3)	-5(3)	-144(3)
O(4)	264(4)	349(4)	315(4)	-11(3)	91(3)	-61(3)
O(5)	302(4)	311(4)	233(3)	-56(3)	7(3)	6(3)
N(1)	200(4)	232(4)	193(4)	-25(3)	-6(3)	-33(3)
N(2)	200(4)	185(4)	260(4)	-25(3)	-40(3)	-11(3)
N(3)	208(4)	209(4)	234(4)	0(3)	21(3)	31(3)
C(1)	173(4)	157(4)	211(4)	-1(3)	-11(3)	9(3)
C(2)	167(4)	154(4)	224(4)	-16(3)	-33(3)	-7(3)
C(3)	161(4)	159(4)	256(4)	7(3)	-4(3)	4(3)
C(4)	188(4)	171(4)	203(4)	12(3)	13(3)	20(3)
C(5)	188(4)	187(4)	212(4)	-5(3)	-25(3)	-3(3)
C(6)	163(4)	197(4)	224(4)	-7(3)	-16(3)	-23(3)
C(7)	215(4)	175(4)	223(4)	8(3)	18(3)	12(3)
C(8)	288(5)	269(5)	217(4)	-22(4)	38(4)	-4(4)

Table 5. Hydrogen coordinates ($x10^3$) and isotropic displacement parameters ($Å^2 \times 10^3$) for 03srv055.

	x	y	z	U(iso)
H(1)	427(2)	149(1)	782(2)	34(4)
H(3)	853(2)	185(1)	426(1)	29(3)
H(5)	321(2)	53(1)	274(1)	23(3)
H(6)	172(2)	56(1)	488(1)	30(3)
H(81)	-14(3)	73(1)	944(2)	53(5)
H(82)	239(3)	88(1)	967(2)	55(5)
H(83)	87(3)	161(1)	926(2)	45(4)

Table 1. Crystal data and structure refinement for (3,5-dinitrobenzyl)-3-trifluoromethylbenzoate

Identification code	04srv099	
Empirical formula	C15 H9 F3 N2 O6	
Formula weight	370.24	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.9267(4) Å	α= 72.299(2)°.
	b = 8.4462(4) Å	β= 74.631(2)°.
	c = 13.1016(6) Å	γ = 63.413(2)°.
Volume	738.66(6) $Å^3$	
Z	2	
Density (calculated)	1.665 Mg/m^3	
Absorption coefficient	0.153 mm^{-1}	
F(000)	376	
Crystal size	0.24 x 0.20 x 0.19 mm^3	
Theta range for data collection	1.65 to 27.45°.	
Index ranges	-9<=h<=10, -10<=k<=10, -16<=l<=16	
Reflections collected	3472	
Independent reflections	2696 [R(int) = 0.0154]	
Completeness to theta = 27.45°	80.1 %	
Absorption correction	None	
Max. and min. transmission	. and .	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2696 / 0 / 235	
Goodness-of-fit on F^2	1.023	
Final R indices [I>2sigma(I)]	R1 = 0.0534, wR2 = 0.1393	
R indices (all data)	R1 = 0.0697, wR2 = 0.1525	
Extinction coefficient	0	
Largest diff. peak and hole	0.651 and -0.258 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 04srv099. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(2)	3344(2)	8368(2)	2080(1)	25(1)
O(3)	3678(3)	2336(2)	3588(2)	35(1)
O(4)	5569(3)	82(2)	2822(2)	38(1)
O(1)	2794(3)	11259(2)	1240(2)	38(1)
C(14)	7658(3)	3409(3)	385(2)	24(1)
N(1)	4900(3)	1684(3)	2864(2)	26(1)
C(6)	674(3)	10656(3)	2829(2)	21(1)
C(13)	6971(3)	2215(3)	1161(2)	25(1)
C(5)	-147(3)	9442(3)	3445(2)	23(1)
O(5)	9138(3)	1433(3)	-785(2)	45(1)
N(2)	9069(3)	2765(3)	-541(2)	33(1)
F(2)	-3627(3)	15956(2)	3605(2)	50(1)
O(6)	10036(3)	3612(3)	-1054(2)	49(1)
C(8)	2349(3)	10159(3)	1966(2)	23(1)
C(12)	5629(3)	2910(3)	1992(2)	21(1)
F(1)	-827(3)	15339(3)	3834(2)	65(1)
F(3)	-2810(3)	14695(2)	5169(1)	55(1)
C(3)	-2350(3)	11675(3)	4485(2)	25(1)
C(10)	5639(3)	5874(3)	1266(2)	21(1)
C(15)	7044(3)	5201(3)	425(2)	23(1)
C(4)	-1674(3)	9969(3)	4258(2)	26(1)
C(9)	5005(4)	7836(3)	1273(2)	28(1)
C(2)	-1501(3)	12874(3)	3868(2)	23(1)
C(11)	4923(3)	4717(3)	2072(2)	21(1)
C(7)	-17(3)	12380(3)	3031(2)	22(1)
C(1)	-2186(4)	14708(3)	4120(2)	30(1)

Table 3. Bond lengths [Å] and angles [57] for 04srv099.

O(2)-C(8)	1.338(3)	C(11)-H(11A)	0.9500
O(2)-C(9)	1.441(3)	C(7)-H(7A)	0.9500
O(3)-N(1)	1.223(3)		
O(4)-N(1)	1.226(3)	C(8)-O(2)-C(9)	114.78(17)
O(1)-C(8)	1.213(3)	C(15)-C(14)-C(13)	123.1(2)
C(14)-C(15)	1.381(3)	C(15)-C(14)-N(2)	117.9(2)
C(14)-C(13)	1.386(3)	C(13)-C(14)-N(2)	118.9(2)
C(14)-N(2)	1.469(3)	O(3)-N(1)-O(4)	124.4(2)
N(1)-C(12)	1.476(3)	O(3)-N(1)-C(12)	117.57(18)
C(6)-C(7)	1.391(3)	O(4)-N(1)-C(12)	118.1(2)
C(6)-C(5)	1.394(3)	C(7)-C(6)-C(5)	120.5(2)
C(6)-C(8)	1.487(3)	C(7)-C(6)-C(8)	117.24(19)
C(13)-C(12)	1.370(3)	C(5)-C(6)-C(8)	122.2(2)
C(13)-H(13A)	0.9500	C(12)-C(13)-C(14)	116.1(2)
C(5)-C(4)	1.386(3)	C(12)-C(13)-H(13A)	122.0
C(5)-H(5A)	0.9500	C(14)-C(13)-H(13A)	122.0
O(5)-N(2)	1.234(3)	C(4)-C(5)-C(6)	119.5(2)
N(2)-O(6)	1.215(3)	C(4)-C(5)-H(5A)	120.2
F(2)-C(1)	1.330(3)	C(6)-C(5)-H(5A)	120.2
C(12)-C(11)	1.399(3)	O(6)-N(2)-O(5)	123.7(2)
F(1)-C(1)	1.328(3)	O(6)-N(2)-C(14)	118.6(2)
F(3)-C(1)	1.330(3)	O(5)-N(2)-C(14)	117.6(2)
C(3)-C(4)	1.392(3)	O(1)-C(8)-O(2)	123.0(2)
C(3)-C(2)	1.398(3)	O(1)-C(8)-C(6)	123.8(2)
C(3)-H(3A)	0.9500	O(2)-C(8)-C(6)	113.19(18)
C(10)-C(15)	1.393(3)	C(13)-C(12)-C(11)	123.7(2)
C(10)-C(11)	1.394(3)	C(13)-C(12)-N(1)	118.53(19)
C(10)-C(9)	1.503(3)	C(11)-C(12)-N(1)	117.7(2)
C(15)-H(15A)	0.9500	C(4)-C(3)-C(2)	119.4(2)
C(4)-H(4A)	0.9500	C(4)-C(3)-H(3A)	120.3
C(9)-H(9A)	0.9900	C(2)-C(3)-H(3A)	120.3
C(9)-H(9B)	0.9900	C(15)-C(10)-C(11)	119.6(2)
C(2)-C(7)	1.384(3)	C(15)-C(10)-C(9)	117.43(19)
C(2)-C(1)	1.506(3)	C(11)-C(10)-C(9)	122.9(2)

C(14)-C(15)-C(10)	119.2(2)
C(14)-C(15)-H(15A)	120.4
C(10)-C(15)-H(15A)	120.4
C(5)-C(4)-C(3)	120.5(2)
C(5)-C(4)-H(4A)	119.7
C(3)-C(4)-H(4A)	119.7
O(2)-C(9)-C(10)	109.67(17)
O(2)-C(9)-H(9A)	109.7
C(10)-C(9)-H(9A)	109.7
O(2)-C(9)-H(9B)	109.7
C(10)-C(9)-H(9B)	109.7
H(9A)-C(9)-H(9B)	108.2
C(7)-C(2)-C(3)	120.4(2)
C(7)-C(2)-C(1)	119.5(2)
C(3)-C(2)-C(1)	120.0(2)
C(10)-C(11)-C(12)	118.1(2)
C(10)-C(11)-H(11A)	120.9
C(12)-C(11)-H(11A)	120.9
C(2)-C(7)-C(6)	119.6(2)
C(2)-C(7)-H(7A)	120.2
C(6)-C(7)-H(7A)	120.2
F(1)-C(1)-F(3)	106.8(2)
F(1)-C(1)-F(2)	106.1(2)
F(3)-C(1)-F(2)	106.0(2)
F(1)-C(1)-C(2)	112.3(2)
F(3)-C(1)-C(2)	112.6(2)
F(2)-C(1)-C(2)	112.5(2)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 04srv099. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(2)	28(1)	18(1)	23(1)	-7(1)	10(1)	-10(1)
O(3)	35(1)	33(1)	33(1)	-6(1)	9(1)	-20(1)
O(4)	51(1)	23(1)	43(1)	-4(1)	-4(1)	-21(1)
O(1)	44(1)	18(1)	32(1)	-4(1)	17(1)	-10(1)
C(14)	24(1)	25(1)	19(1)	-10(1)	3(1)	-6(1)
N(1)	28(1)	24(1)	29(1)	-5(1)	-1(1)	-15(1)
C(6)	23(1)	21(1)	17(1)	-4(1)	0(1)	-9(1)
C(13)	26(1)	19(1)	27(1)	-10(1)	-1(1)	-7(1)
C(5)	24(1)	21(1)	21(1)	-3(1)	1(1)	-10(1)
O(5)	52(1)	37(1)	37(1)	-21(1)	2(1)	-7(1)
N(2)	34(1)	28(1)	27(1)	-12(1)	5(1)	-4(1)
F(2)	57(1)	26(1)	60(1)	-18(1)	-22(1)	3(1)
O(6)	45(1)	50(1)	42(1)	-21(1)	23(1)	-21(1)
C(8)	27(1)	19(1)	21(1)	-6(1)	4(1)	-10(1)
C(12)	22(1)	24(1)	19(1)	-5(1)	-1(1)	-13(1)
F(1)	46(1)	58(1)	110(2)	-60(1)	26(1)	-30(1)
F(3)	84(2)	41(1)	32(1)	-22(1)	1(1)	-15(1)
C(3)	19(1)	33(1)	21(1)	-8(1)	2(1)	-8(1)
C(10)	22(1)	20(1)	21(1)	-6(1)	2(1)	-10(1)
C(15)	24(1)	22(1)	19(1)	-4(1)	2(1)	-10(1)
C(4)	24(1)	30(1)	20(1)	-1(1)	-1(1)	-14(1)
C(9)	30(1)	21(1)	27(1)	-10(1)	14(1)	-13(1)
C(2)	22(1)	24(1)	22(1)	-8(1)	-2(1)	-7(1)
C(11)	22(1)	20(1)	21(1)	-7(1)	4(1)	-11(1)
C(7)	22(1)	20(1)	21(1)	-5(1)	1(1)	-8(1)
C(1)	28(1)	31(1)	31(1)	-17(1)	3(1)	-8(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 04srv099.

	x	y	z	U(eq)
H(13A)	7406	987	1119	30
H(5A)	336	8262	3309	27
H(3A)	-3379	12022	5053	30
H(15A)	7574	5967	-115	27
H(4A)	-2263	9159	4664	31
H(9A)	6048	8019	1435	33
H(9B)	4699	8595	550	33
H(11A)	3982	5144	2659	25
H(7A)	527	13213	2598	26

Table 1. Crystal data and structure refinement for (3,5-dinitrobenzyl)-4-trifluoromethylbenzoate.

Identification code	04srv064	
Empirical formula	C15 H9 F3 N2 O6	
Formula weight	370.24	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 10.0032(4) Å	α= 90.924(2)°.
	b = 14.9048(6) Å	β= 99.989(2)°.
	c = 15.3342(6) Å	γ = 91.005(2)°.
Volume	2250.83(16) $Å^3$	
Z	6	
Density (calculated)	1.639 Mg/m^3	
Absorption coefficient	0.151 mm^{-1}	
F(000)	1128	
Crystal size	0.17 x 0.17 x 0.03 mm^3	
Theta range for data collection	1.35 to 27.44°.	
Index ranges	-12<=h<=12, -19<=k<=16, -19<=l<=19	
Reflections collected	20040	
Independent reflections	10198 [R(int) = 0.0274]	
Completeness to theta = 27.44°	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.997 and 0.970	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	10198 / 0 / 712	
Goodness-of-fit on F^2	1.049	
Final R indices [I>2sigma(I)]	R1 = 0.0737, wR2 = 0.2026	
R indices (all data)	R1 = 0.0947, wR2 = 0.2196	
Extinction coefficient	0	
Largest diff. peak and hole	0.970 and -0.514 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 04srv064. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(7A)	370(2)	5728(1)	-1125(2)	56(1)
F(7B)	2489(2)	5848(2)	-1061(2)	54(1)
F(7C)	1686(3)	5004(1)	-166(1)	68(1)
C(7)	1552(3)	5776(2)	-548(2)	28(1)
C(4)	1595(3)	6559(2)	83(2)	24(1)
C(3)	1634(3)	7417(2)	-254(2)	26(1)
C(5)	1574(3)	6429(2)	975(2)	25(1)
C(2)	1670(3)	8152(2)	310(2)	24(1)
C(6)	1608(3)	7167(2)	1538(2)	25(1)
C(1)	1657(3)	8034(2)	1210(2)	21(1)
C(8)	1705(3)	8803(2)	1843(2)	24(1)
O(8A)	1768(3)	8739(1)	2629(1)	46(1)
O(8B)	1663(2)	9595(1)	1434(1)	21(1)
C(9)	1727(3)	10365(2)	2016(2)	25(1)
C(10)	1811(3)	11205(2)	1493(2)	20(1)
C(11)	1764(3)	11199(2)	582(2)	21(1)
C(15)	1955(3)	12023(2)	1966(2)	20(1)
C(12)	1865(3)	12018(2)	166(2)	21(1)
C(14)	2069(3)	12809(2)	1512(2)	20(1)
C(13)	2049(3)	12832(2)	612(2)	23(1)
N(1)	2278(2)	13658(1)	2030(2)	23(1)
O(1A)	2135(2)	13649(1)	2807(1)	27(1)
O(1B)	2597(2)	14329(1)	1650(1)	34(1)
N(2)	1770(2)	12011(2)	-802(2)	27(1)
O(2A)	1891(3)	12738(2)	-1154(1)	38(1)
O(2B)	1538(3)	11297(2)	-1209(1)	37(1)
F(22A)	6586(2)	1(1)	1936(2)	57(1)
F(22B)	6171(3)	737(1)	754(2)	73(1)
F(22C)	4549(2)	71(1)	1290(2)	48(1)
C(22)	5687(3)	564(2)	1477(2)	34(1)
C(19)	5519(3)	1394(2)	2017(2)	24(1)

C(18)	5645(3)	2241(2)	1664(2)	24(1)
C(20)	5224(3)	1299(2)	2862(2)	23(1)
C(17)	5501(3)	2998(2)	2176(2)	20(1)
C(21)	5058(3)	2053(2)	3367(2)	19(1)
C(16)	5212(2)	2908(2)	3028(2)	16(1)
C(23)	5046(2)	3695(2)	3604(2)	17(1)
O(23A)	4863(2)	3642(1)	4362(1)	26(1)
O(23B)	5119(2)	4473(1)	3187(1)	19(1)
C(24)	4914(3)	5255(2)	3711(2)	22(1)
C(25)	5026(2)	6080(2)	3174(2)	18(1)
C(26)	5056(2)	6058(2)	2274(2)	19(1)
C(30)	5067(3)	6901(2)	3623(2)	19(1)
C(27)	5128(3)	6868(2)	1842(2)	21(1)
C(29)	5120(3)	7683(2)	3158(2)	21(1)
C(28)	5159(3)	7694(2)	2260(2)	23(1)
N(3)	5114(3)	8539(2)	3639(2)	33(1)
O(3A)	5141(2)	8546(1)	4434(1)	31(1)
O(3C)	4715(7)	9211(4)	3169(5)	41(2)
O(3B)	5494(9)	9223(4)	3273(5)	54(2)
N(4)	5150(3)	6846(2)	882(2)	29(1)
O(4A)	5147(3)	7571(2)	513(1)	40(1)
O(4B)	5165(3)	6121(2)	512(2)	46(1)
F(37A)	7843(2)	5099(1)	2936(2)	45(1)
F(37B)	9505(2)	5753(1)	2459(1)	46(1)
F(37C)	9846(2)	5009(1)	3655(1)	38(1)
C(37)	8999(3)	5574(2)	3184(2)	24(1)
C(34)	8786(3)	6404(2)	3708(2)	20(1)
C(33)	8822(3)	7247(2)	3335(2)	21(1)
C(35)	8525(3)	6310(2)	4564(2)	22(1)
C(32)	8612(3)	8006(2)	3832(2)	20(1)
C(36)	8315(3)	7067(2)	5058(2)	20(1)
C(31)	8366(2)	7916(2)	4695(2)	17(1)
C(38)	8164(3)	8703(2)	5264(2)	19(1)
O(38A)	8017(2)	8649(1)	6025(1)	28(1)
O(38B)	8186(2)	9490(1)	4850(1)	22(1)
C(39)	7932(3)	10249(2)	5380(2)	28(1)

C(40)	8115(3)	11099(2)	4897(2)	19(1)
C(41)	8416(3)	11118(2)	4048(2)	20(1)
C(45)	7971(3)	11904(2)	5347(2)	19(1)
C(42)	8577(2)	11951(2)	3669(2)	19(1)
C(44)	8106(2)	12706(2)	4928(2)	18(1)
C(43)	8416(3)	12759(2)	4086(2)	21(1)
N(5)	7905(2)	13545(1)	5398(2)	23(1)
O(5A)	7831(2)	13516(1)	6182(1)	28(1)
O(5B)	7810(2)	14237(1)	4971(2)	33(1)
N(6)	8919(2)	11977(2)	2778(2)	25(1)
O(6A)	9148(3)	12715(1)	2487(2)	38(1)
O(6B)	8953(2)	11270(1)	2366(1)	31(1)

Table 4. Bond lengths [Å] and angles [57] for 04srv064.

F(7A)-C(7)	
F(7B)-C(7)	1.328(3)
F(7C)-C(7)	1.298(3)
C(7)-C(4)	1.499(4)
C(4)-C(5)	1.389(4)
C(4)-C(3)	1.390(4)
C(3)-C(2)	1.380(4)
C(3)-H(3)	0.9500
C(5)-C(6)	1.383(4)
C(5)-H(5)	0.9500
C(2)-C(1)	1.397(4)
C(2)-H(2)	0.9500
C(6)-C(1)	1.398(3)
C(6)-H(6)	0.9500
C(1)-C(8)	1.484(4)
C(8)-O(8A)	1.201(3)
C(8)-O(8B)	1.343(3)
O(8B)-C(9)	1.436(3)
C(9)-C(10)	1.507(3)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900

C(10)-C(11)	1.390(4)
C(10)-C(15)	1.400(3)
C(11)-C(12)	1.396(3)
C(11)-H(11)	0.9500
C(15)-C(14)	1.385(3)
C(15)-H(15)	0.9500
C(12)-C(13)	1.376(4)
C(12)-N(2)	1.471(3)
C(14)-C(13)	1.379(4)
C(14)-N(1)	1.476(3)
C(13)-H(13)	0.9500
N(1)-O(1A)	1.226(3)
N(1)-O(1B)	1.230(3)
N(2)-O(2B)	1.223(3)
N(2)-O(2A)	1.231(3)
F(22A)-C(22)	1.354(4)
F(22B)-C(22)	1.312(4)
F(22C)-C(22)	1.329(4)
C(22)-C(19)	1.506(4)
C(19)-C(20)	1.388(4)
C(19)-C(18)	1.394(4)
C(18)-C(17)	1.387(4)
C(18)-H(18)	0.9500
C(20)-C(21)	1.384(3)
C(20)-H(20)	0.9500
C(17)-C(16)	1.394(3)
C(17)-H(17)	0.9500
C(21)-C(16)	1.399(3)
C(21)-H(21)	0.9500
C(16)-C(23)	1.486(3)
C(23)-O(23A)	1.210(3)
C(23)-O(23B)	1.339(3)
O(23B)-C(24)	1.442(3)
C(24)-C(25)	1.504(3)
C(24)-H(24A)	0.9900
C(24)-H(24B)	0.9900

C(25)-C(26)	1.385(3)
C(25)-C(30)	1.391(3)
C(26)-C(27)	1.393(3)
C(26)-H(26)	0.9500
C(30)-C(29)	1.380(3)
C(30)-H(30)	0.9500
C(27)-C(28)	1.377(4)
C(27)-N(4)	1.476(3)
C(29)-C(28)	1.385(4)
C(29)-N(3)	1.464(3)
C(28)-H(28)	0.9500
N(3)-O(3A)	1.214(3)
N(3)-O(3B)	1.255(7)
N(3)-O(3C)	1.273(7)
N(4)-O(4B)	1.214(3)
N(4)-O(4A)	1.228(3)
F(37A)-C(37)	1.339(3)
F(37B)-C(37)	1.328(3)
F(37C)-C(37)	1.334(3)
C(37)-C(34)	1.503(3)
C(34)-C(35)	1.392(4)
C(34)-C(33)	1.392(3)
C(33)-C(32)	1.392(3)
C(33)-H(33)	0.9500
C(35)-C(36)	1.387(3)
C(35)-H(35)	0.9500
C(32)-C(31)	1.396(3)
C(32)-H(32)	0.9500
C(36)-C(31)	1.394(3)
C(36)-H(36)	0.9500
C(31)-C(38)	1.489(3)
C(38)-O(38A)	1.205(3)
C(38)-O(38B)	1.344(3)
O(38B)-C(39)	1.434(3)
C(39)-C(40)	1.502(3)
C(39)-H(39B)	0.9900

C(39)-H(39A)	0.9900
C(40)-C(41)	1.387(4)
C(40)-C(45)	1.396(3)
C(41)-C(42)	1.397(3)
C(41)-H(41)	0.9500
C(45)-C(44)	1.382(3)
C(45)-H(45)	0.9500
C(42)-C(43)	1.380(3)
C(42)-N(6)	1.465(3)
C(44)-C(43)	1.382(4)
C(44)-N(5)	1.469(3)
C(43)-H(43)	0.9500
N(5)-O(5A)	1.217(3)
N(5)-O(5B)	1.227(3)
N(6)-O(6B)	1.224(3)
N(6)-O(6A)	1.227(3)

F(7C)-C(7)-F(7B)	108.0(3)
F(7C)-C(7)-F(7A)	106.5(3)
F(7B)-C(7)-F(7A)	104.0(3)
F(7C)-C(7)-C(4)	114.0(2)
F(7B)-C(7)-C(4)	112.2(2)
F(7A)-C(7)-C(4)	111.5(2)
C(5)-C(4)-C(3)	121.0(2)
C(5)-C(4)-C(7)	120.9(2)
C(3)-C(4)-C(7)	118.1(2)
C(2)-C(3)-C(4)	119.5(2)
C(2)-C(3)-H(3)	120.3
C(4)-C(3)-H(3)	120.3
C(6)-C(5)-C(4)	119.4(2)
C(6)-C(5)-H(5)	120.3
C(4)-C(5)-H(5)	120.3
C(3)-C(2)-C(1)	120.3(2)
C(3)-C(2)-H(2)	119.8
C(1)-C(2)-H(2)	119.8
C(5)-C(6)-C(1)	120.2(2)

C(5)-C(6)-H(6)	119.9
C(1)-C(6)-H(6)	119.9
C(2)-C(1)-C(6)	119.6(2)
C(2)-C(1)-C(8)	122.2(2)
C(6)-C(1)-C(8)	118.2(2)
O(8A)-C(8)-O(8B)	123.1(2)
O(8A)-C(8)-C(1)	124.9(2)
O(8B)-C(8)-C(1)	112.0(2)
C(8)-O(8B)-C(9)	114.5(2)
O(8B)-C(9)-C(10)	109.4(2)
O(8B)-C(9)-H(9A)	109.8
C(10)-C(9)-H(9A)	109.8
O(8B)-C(9)-H(9B)	109.8
C(10)-C(9)-H(9B)	109.8
H(9A)-C(9)-H(9B)	108.3
C(11)-C(10)-C(15)	119.6(2)
C(11)-C(10)-C(9)	123.3(2)
C(15)-C(10)-C(9)	117.2(2)
C(10)-C(11)-C(12)	118.4(2)
C(10)-C(11)-H(11)	120.8
C(12)-C(11)-H(11)	120.8
C(14)-C(15)-C(10)	118.9(2)
C(14)-C(15)-H(15)	120.5
C(10)-C(15)-H(15)	120.5
C(13)-C(12)-C(11)	123.7(2)
C(13)-C(12)-N(2)	118.1(2)
C(11)-C(12)-N(2)	118.2(2)
C(13)-C(14)-C(15)	123.4(2)
C(13)-C(14)-N(1)	118.6(2)
C(15)-C(14)-N(1)	117.9(2)
C(12)-C(13)-C(14)	116.0(2)
C(12)-C(13)-H(13)	122.0
C(14)-C(13)-H(13)	122.0
O(1A)-N(1)-O(1B)	124.4(2)
O(1A)-N(1)-C(14)	118.2(2)
O(1B)-N(1)-C(14)	117.4(2)

O(2B)-N(2)-O(2A)	124.1(2)
O(2B)-N(2)-C(12)	118.6(2)
O(2A)-N(2)-C(12)	117.3(2)
F(22B)-C(22)-F(22C)	110.8(3)
F(22B)-C(22)-F(22A)	105.1(3)
F(22C)-C(22)-F(22A)	103.7(2)
F(22B)-C(22)-C(19)	113.0(2)
F(22C)-C(22)-C(19)	112.3(2)
F(22A)-C(22)-C(19)	111.2(3)
C(20)-C(19)-C(18)	120.9(2)
C(20)-C(19)-C(22)	118.9(2)
C(18)-C(19)-C(22)	120.2(2)
C(17)-C(18)-C(19)	119.3(2)
C(17)-C(18)-H(18)	120.4
C(19)-C(18)-H(18)	120.4
C(21)-C(20)-C(19)	119.8(2)
C(21)-C(20)-H(20)	120.1
C(19)-C(20)-H(20)	120.1
C(18)-C(17)-C(16)	120.2(2)
C(18)-C(17)-H(17)	119.9
C(16)-C(17)-H(17)	119.9
C(20)-C(21)-C(16)	119.8(2)
C(20)-C(21)-H(21)	120.1
C(16)-C(21)-H(21)	120.1
C(17)-C(16)-C(21)	120.0(2)
C(17)-C(16)-C(23)	122.3(2)
C(21)-C(16)-C(23)	117.6(2)
O(23A)-C(23)-O(23B)	123.8(2)
O(23A)-C(23)-C(16)	124.0(2)
O(23B)-C(23)-C(16)	112.2(2)
C(23)-O(23B)-C(24)	114.10(18)
O(23B)-C(24)-C(25)	108.98(19)
O(23B)-C(24)-H(24A)	109.9
C(25)-C(24)-H(24A)	109.9
O(23B)-C(24)-H(24B)	109.9
C(25)-C(24)-H(24B)	109.9

H(24A)-C(24)-H(24B)	108.3
C(26)-C(25)-C(30)	119.7(2)
C(26)-C(25)-C(24)	123.7(2)
C(30)-C(25)-C(24)	116.6(2)
C(25)-C(26)-C(27)	118.6(2)
C(25)-C(26)-H(26)	120.7
C(27)-C(26)-H(26)	120.7
C(29)-C(30)-C(25)	119.2(2)
C(29)-C(30)-H(30)	120.4
C(25)-C(30)-H(30)	120.4
C(28)-C(27)-C(26)	123.5(2)
C(28)-C(27)-N(4)	117.8(2)
C(26)-C(27)-N(4)	118.7(2)
C(30)-C(29)-C(28)	123.2(2)
C(30)-C(29)-N(3)	118.2(2)
C(28)-C(29)-N(3)	118.6(2)
C(27)-C(28)-C(29)	115.8(2)
C(27)-C(28)-H(28)	122.1
C(29)-C(28)-H(28)	122.1
O(3A)-N(3)-O(3B)	119.9(4)
O(3A)-N(3)-O(3C)	121.7(4)
O(3A)-N(3)-C(29)	119.8(2)
O(3B)-N(3)-C(29)	116.8(4)
O(3C)-N(3)-C(29)	115.8(4)
O(4B)-N(4)-O(4A)	124.5(2)
O(4B)-N(4)-C(27)	118.4(2)
O(4A)-N(4)-C(27)	117.1(2)
F(37B)-C(37)-F(37C)	106.8(2)
F(37B)-C(37)-F(37A)	107.7(2)
F(37C)-C(37)-F(37A)	105.0(2)
F(37B)-C(37)-C(34)	112.8(2)
F(37C)-C(37)-C(34)	112.3(2)
F(37A)-C(37)-C(34)	111.9(2)
C(35)-C(34)-C(33)	120.9(2)
C(35)-C(34)-C(37)	118.6(2)
C(33)-C(34)-C(37)	120.5(2)

C(34)-C(33)-C(32)	119.4(2)
C(34)-C(33)-H(33)	120.3
C(32)-C(33)-H(33)	120.3
C(36)-C(35)-C(34)	119.6(2)
C(36)-C(35)-H(35)	120.2
C(34)-C(35)-H(35)	120.2
C(33)-C(32)-C(31)	120.0(2)
C(33)-C(32)-H(32)	120.0
C(31)-C(32)-H(32)	120.0
C(35)-C(36)-C(31)	120.0(2)
C(35)-C(36)-H(36)	120.0
C(31)-C(36)-H(36)	120.0
C(36)-C(31)-C(32)	120.1(2)
C(36)-C(31)-C(38)	117.5(2)
C(32)-C(31)-C(38)	122.4(2)
O(38A)-C(38)-O(38B)	122.9(2)
O(38A)-C(38)-C(31)	123.8(2)
O(38B)-C(38)-C(31)	113.3(2)
C(38)-O(38B)-C(39)	113.66(19)
O(38B)-C(39)-C(40)	109.7(2)
O(38B)-C(39)-H(39B)	109.7
C(40)-C(39)-H(39B)	109.7
O(38B)-C(39)-H(39A)	109.7
C(40)-C(39)-H(39A)	109.7
H(39B)-C(39)-H(39A)	108.2
C(41)-C(40)-C(45)	119.6(2)
C(41)-C(40)-C(39)	123.7(2)
C(45)-C(40)-C(39)	116.7(2)
C(40)-C(41)-C(42)	118.6(2)
C(40)-C(41)-H(41)	120.7
C(42)-C(41)-H(41)	120.7
C(44)-C(45)-C(40)	119.1(2)
C(44)-C(45)-H(45)	120.5
C(40)-C(45)-H(45)	120.5
C(43)-C(42)-C(41)	123.4(2)
C(43)-C(42)-N(6)	117.7(2)

C(41)-C(42)-N(6)	118.9(2)
C(45)-C(44)-C(43)	123.4(2)
C(45)-C(44)-N(5)	118.4(2)
C(43)-C(44)-N(5)	118.2(2)
C(42)-C(43)-C(44)	115.9(2)
C(42)-C(43)-H(43)	122.1
C(44)-C(43)-H(43)	122.1
O(5A)-N(5)-O(5B)	124.0(2)
O(5A)-N(5)-C(44)	118.6(2)
O(5B)-N(5)-C(44)	117.5(2)
O(6B)-N(6)-O(6A)	123.8(2)
O(6B)-N(6)-C(42)	118.8(2)
O(6A)-N(6)-C(42)	117.5(2)

Symmetry transformations used to generate equivalent atoms:

Table 5. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 04srv064. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(7A)	45(1)	49(1)	66(2)	-33(1)	-12(1)	7(1)
F(7B)	59(1)	51(1)	60(1)	-30(1)	39(1)	-15(1)
F(7C)	153(3)	23(1)	32(1)	1(1)	24(1)	19(1)
C(7)	34(2)	24(1)	27(1)	-1(1)	10(1)	-1(1)
C(4)	26(1)	21(1)	25(1)	-3(1)	8(1)	-2(1)
C(3)	36(2)	23(1)	22(1)	0(1)	11(1)	-2(1)
C(5)	31(1)	18(1)	27(1)	3(1)	9(1)	0(1)
C(2)	33(1)	19(1)	22(1)	2(1)	7(1)	-5(1)
C(6)	33(1)	22(1)	21(1)	4(1)	7(1)	-1(1)
C(1)	24(1)	18(1)	21(1)	0(1)	6(1)	0(1)
C(8)	30(1)	18(1)	25(1)	4(1)	5(1)	0(1)
O(8A)	99(2)	18(1)	20(1)	-1(1)	11(1)	3(1)
O(8B)	31(1)	14(1)	20(1)	0(1)	6(1)	-1(1)
C(9)	37(2)	19(1)	20(1)	0(1)	9(1)	2(1)

C(10)	23(1)	17(1)	22(1)	1(1)	5(1)	3(1)
C(11)	25(1)	19(1)	19(1)	-3(1)	3(1)	2(1)
C(15)	23(1)	19(1)	18(1)	0(1)	4(1)	2(1)
C(12)	23(1)	25(1)	15(1)	1(1)	4(1)	1(1)
C(14)	24(1)	17(1)	20(1)	-2(1)	1(1)	-1(1)
C(13)	23(1)	21(1)	22(1)	6(1)	1(1)	3(1)
N(1)	27(1)	16(1)	24(1)	1(1)	-2(1)	1(1)
O(1A)	37(1)	22(1)	22(1)	-6(1)	5(1)	0(1)
O(1B)	48(1)	18(1)	32(1)	5(1)	-2(1)	-4(1)
N(2)	29(1)	32(1)	19(1)	2(1)	2(1)	5(1)
O(2A)	53(1)	39(1)	21(1)	10(1)	3(1)	-1(1)
O(2B)	56(1)	34(1)	21(1)	-7(1)	8(1)	5(1)
F(22A)	47(1)	33(1)	89(2)	-20(1)	12(1)	11(1)
F(22B)	139(3)	34(1)	63(2)	-16(1)	70(2)	-9(1)
F(22C)	41(1)	38(1)	62(1)	-30(1)	5(1)	-4(1)
C(22)	43(2)	23(1)	41(2)	-10(1)	24(1)	-6(1)
C(19)	28(1)	17(1)	29(1)	-5(1)	10(1)	-2(1)
C(18)	30(1)	22(1)	21(1)	-1(1)	12(1)	-3(1)
C(20)	29(1)	14(1)	27(1)	1(1)	9(1)	-1(1)
C(17)	22(1)	18(1)	20(1)	3(1)	5(1)	-1(1)
C(21)	25(1)	15(1)	18(1)	1(1)	4(1)	-1(1)
C(16)	16(1)	14(1)	18(1)	1(1)	2(1)	0(1)
C(23)	20(1)	13(1)	17(1)	1(1)	0(1)	-2(1)
O(23A)	47(1)	16(1)	16(1)	0(1)	7(1)	-1(1)
O(23B)	28(1)	11(1)	18(1)	0(1)	7(1)	0(1)
C(24)	37(2)	12(1)	18(1)	-1(1)	10(1)	1(1)
C(25)	19(1)	15(1)	21(1)	2(1)	4(1)	0(1)
C(26)	19(1)	19(1)	21(1)	-1(1)	4(1)	1(1)
C(30)	23(1)	16(1)	19(1)	2(1)	5(1)	0(1)
C(27)	20(1)	26(1)	17(1)	5(1)	3(1)	1(1)
C(29)	26(1)	15(1)	23(1)	2(1)	6(1)	0(1)
C(28)	29(1)	20(1)	22(1)	7(1)	6(1)	2(1)
N(3)	58(2)	13(1)	29(1)	2(1)	10(1)	0(1)
O(3A)	44(1)	21(1)	30(1)	-4(1)	9(1)	3(1)
O(3C)	68(4)	14(2)	42(3)	10(2)	11(3)	5(3)
O(3B)	117(6)	13(2)	32(3)	6(2)	9(4)	1(4)

N(4)	34(1)	35(1)	19(1)	2(1)	6(1)	-1(1)
O(4A)	55(2)	44(1)	23(1)	15(1)	10(1)	5(1)
O(4B)	75(2)	42(1)	24(1)	-4(1)	17(1)	-3(1)
F(37A)	31(1)	35(1)	66(1)	-31(1)	2(1)	-4(1)
F(37B)	84(2)	27(1)	36(1)	-8(1)	32(1)	3(1)
F(37C)	44(1)	25(1)	43(1)	-7(1)	3(1)	12(1)
C(37)	26(1)	19(1)	28(1)	-6(1)	4(1)	-1(1)
C(34)	23(1)	15(1)	22(1)	-4(1)	4(1)	0(1)
C(33)	29(1)	20(1)	16(1)	-2(1)	5(1)	1(1)
C(35)	28(1)	14(1)	23(1)	1(1)	6(1)	-3(1)
C(32)	26(1)	14(1)	21(1)	2(1)	6(1)	1(1)
C(36)	25(1)	16(1)	19(1)	1(1)	7(1)	-2(1)
C(31)	19(1)	15(1)	18(1)	-2(1)	2(1)	-1(1)
C(38)	24(1)	15(1)	19(1)	1(1)	5(1)	0(1)
O(38A)	49(1)	18(1)	20(1)	-1(1)	13(1)	0(1)
O(38B)	36(1)	11(1)	20(1)	-1(1)	9(1)	2(1)
C(39)	51(2)	14(1)	23(1)	0(1)	17(1)	4(1)
C(40)	24(1)	13(1)	21(1)	1(1)	5(1)	2(1)
C(41)	21(1)	19(1)	21(1)	-2(1)	4(1)	1(1)
C(45)	23(1)	17(1)	19(1)	2(1)	5(1)	3(1)
C(42)	17(1)	23(1)	17(1)	0(1)	4(1)	1(1)
C(44)	17(1)	15(1)	22(1)	-3(1)	2(1)	2(1)
C(43)	21(1)	19(1)	23(1)	4(1)	4(1)	1(1)
N(5)	25(1)	15(1)	28(1)	0(1)	5(1)	0(1)
O(5A)	37(1)	21(1)	25(1)	-5(1)	9(1)	3(1)
O(5B)	47(1)	14(1)	38(1)	4(1)	7(1)	2(1)
N(6)	25(1)	29(1)	22(1)	1(1)	8(1)	-1(1)
O(6A)	55(1)	31(1)	32(1)	8(1)	22(1)	-2(1)
O(6B)	36(1)	34(1)	26(1)	-7(1)	12(1)	0(1)

Table 6. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 04srv064.

	x	y	z	U(eq)

H(3)	1637	7498	-867	31
H(5)	1536	5839	1197	30
H(2)	1703	8740	84	29
H(6)	1598	7083	2150	30
H(9A)	2534	10332	2489	30
H(9B)	908	10376	2298	30
H(11)	1667	10651	250	26
H(15)	1975	12038	2588	24
H(13)	2156	13377	316	27
H(18)	5828	2300	1080	28
H(20)	5136	717	3094	27
H(17)	5600	3578	1946	23
H(21)	4840	1992	3942	23
H(24A)	5606	5284	4257	26
H(24B)	4006	5219	3883	26
H(26)	5027	5503	1958	23
H(30)	5059	6924	4241	22
H(28)	5204	8239	1951	28
H(33)	8988	7305	2746	26
H(35)	8492	5730	4810	26
H(32)	8637	8584	3583	25
H(36)	8137	7006	5643	23
H(39B)	8569	10253	5952	34
H(39A)	6995	10207	5505	34
H(41)	8512	10577	3731	24
H(45)	7782	11900	5933	23
H(43)	8513	13317	3811	25

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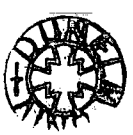

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